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Ab interno trabecular bypass surgery with iStent for open-angle glaucoma (Review)

Le JT, Bicket AK, Wang L, Li T

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Ab interno trabecular bypass surgery with iStent for open-angle glaucoma.
Cochrane Database of Systematic Reviews 2019, Issue 3. Art. No.: CD012743.
DOI: 10.1002/14651858.CD012743.pub2.

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[Intervention Review]

Ab interno trabecular bypass surgery with iStent for open-angle glaucoma

Jimmy T Le[1], Amanda K Bicket[2], Lin Wang[1], Tianjing Li[1]

[1]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA. [2]Department of Ophthalmology, Wilmer Eye Institute, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

Contact address: Jimmy T Le, Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, 615 N. Wolfe Street, E6009, Baltimore, Maryland, 21205, USA. jle6@jhu.edu.

Editorial group: Cochrane Eyes and Vision Group.
Publication status and date: New, published in Issue 3, 2019.

Citation: Le JT, Bicket AK, Wang L, Li T. Ab interno trabecular bypass surgery with iStent for open-angle glaucoma. *Cochrane Database of Systematic Reviews* 2019, Issue 3. Art. No.: CD012743. DOI: 10.1002/14651858.CD012743.pub2.

ABSTRACT

Background

Glaucoma is a leading cause of irreversible blindness worldwide. In early stages, glaucoma results in progressive loss of peripheral (side) vision; in later stages, it results in loss of central vision leading to blindness. Elevated intraocular pressure (IOP) is the only known modifiable risk factor for glaucoma. Minimally invasive glaucoma surgical (MIGS) techniques, such as ab interno trabecular bypass surgery with iStent (Glaukos Corporation, Laguna Hills, CA, USA), have been introduced as a new treatment modality for glaucoma. However, the effectiveness of MIGS on keeping people 'drop-free' (i.e. not having to use eye drops to control IOP) and other outcomes is uncertain.

Objectives

To assess the effectiveness and safety of ab interno trabecular bypass surgery with iStent (or iStent inject) for open-angle glaucoma in comparison to conventional medical, laser, or surgical treatment.

Search methods

Cochrane Eyes and Vision's Information Specialist searched the following databases on 17 August 2018: the Cochrane Central Register of Controlled Trials (CENTRAL) (which contains the Cochrane Eyes and Vision Trials Register; 2018, Issue 7), MEDLINE Ovid, Embase Ovid, the ISRCTN registry, ClinicalTrials.gov, and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP). We applied no date or language restrictions. We searched the reference lists of reports from included studies.

Selection criteria

We included randomized controlled trials (RCTs) that had compared iStent or iStent inject to medical therapy, laser treatment, conventional glaucoma surgery (trabeculectomy), or other MIGS procedures. We included RCTs that had compared iStent or iStent inject in combination with phacoemulsification to phacoemulsification alone.

Data collection and analysis

We used standard methodological procedures expected by Cochrane. Two review authors independently screened search results, assessed risk of bias, and extracted data from reports of included RCTs using an electronic data collection form.

Main results

We included seven RCTs (765 eyes of 764 participants; range per study 33 to 239 participants) that evaluated iStent in people with open-angle glaucoma. We also identified 13 studies that are ongoing or awaiting publications of results. Most participants in the included studies were women (417/764 (55%) participants) and older age (age range: 49 to 89 years). We assessed most trials at unclear or high risk of bias:

four trials did not clearly report the method of generating the random sequence or concealing allocation; five were unmasked, open-label studies, which we assessed at high risk of bias for performance and detection bias. All seven trials were funded by the Glaukos Corporation. We graded the certainty of evidence as very low.

Four RCTs compared iStent in combination with phacoemulsification to phacoemulsification alone. The summary estimate which we derived from two of the four RCTs suggested that participants in the iStent in combination with phacoemulsification group were 1.38 times more likely to be drop-free between six and 18 months than those in the phacoemulsification alone group (risk ratio (RR) 1.38, 95% confidence interval (CI) 1.18 to 1.63, I^2 = 67%). Data from two RCTs also suggested that iStent in combination with phacoemulsification compared to phacoemulsification alone may have offered a small reduction in number of IOP-lowering drops (mean difference (MD) −0.42 drops, 95% CI −0.60 to −0.23). It is uncertain whether there was any difference in terms of mean reduction in IOP from baseline (no meta-analysis).

Two RCTs compared treatment with iStent to medical therapy; one of the two trials used the iStent inject. We determined the two trials to be clinically and methodologically heterogeneous and did not conduct a meta-analysis; however, the investigators of both trials reported that over 90% of participants in the treatment groups were drop-free compared to no participants in the medical therapy groups at six to 18 months.

One RCT compared treatment with one versus two versus three iStents. There was no difference in terms of participants who were drop-free at 36 months or less; however, at longer follow-up (i.e. at 42 months) participants in the one iStent treatment were less likely to be drop-free than those in the two iStent (RR 0.51, 95% CI 0.34 to 0.75) or three iStent (RR 0.49, 95% CI 0.34 to 0.73) treatment groups. The study did not report the mean change in number of IOP-lowering drops.

The type and timing of complications reported varied by RCTs. Similar proportions of participants who underwent treatment with iStent in combination with phacoemulsification and who underwent phacoemulsification alone needed secondary glaucoma surgery. None of RCTs reported findings related to quality of life.

Authors' conclusions

There is very low-quality evidence that treatment with iStent may result in higher proportions of participants who are drop-free or achieving better IOP control, in the short, medium, or long-term. Results from the 13 studies with results not yet available may clarify the benefits of treatment of people with iStent. Additionally, future MIGS studies should consider measuring quality of life and outcomes that reflect people's ability to perform vision-dependent activities.

PLAIN LANGUAGE SUMMARY

iStent for open-angle glaucoma

What was the aim of this review?
The aim of this Cochrane Review was to find out whether the implantation of one or more iStent or iStent inject devices ('iStents'), compared with conventional medical, laser, or surgical treatments, can keep people who have primary open-angle glaucoma from needing to use glaucoma drops (i.e. keep them 'drop-free'). The glaucoma drops are used to control the fluid pressure within their eyes (called the intraocular pressure (IOP)). We also looked at average change from baseline in number of glaucoma drops needed to control IOP, average change from baseline (i.e. before treatment) in IOP, and health-related quality of life as defined by study investigators. We examined all outcomes at short-term (less than six months), medium-term (six to ≤ 18 months), long-term (> 18 months and ≤ 36 months) and greater than 36-month time points. We collected and analyzed all relevant randomized controlled trials (RCTs; clinical studies where people are randomly put into one of two or more treatment groups) to answer this question and found seven RCTs evaluating iStents.

Key messages
There was very low-quality evidence that treatment with iStents may have resulted in higher proportions of people who were drop-free at medium-term time points or who had better control of their IOP. None of the seven RCTs examined how the iStent affected quality of life and reporting on complications was highly variable. At present, clinical practice decisions should be based on provider judgment and patient preferences, given inconsistency in results and risk of bias in relevant studies published to date.

What did we study in this review?
Glaucoma is a group of eye diseases that cause irreversible damage to the optic nerve in the eye. If untreated, glaucoma can lead to blindness. Elevated IOP is the only known modifiable risk factor for open-angle glaucoma, which is the most common form of glaucoma. Conventional first-choice treatments for open-angle glaucoma include medical (e.g. glaucoma drops) or laser interventions. Surgery, which has a higher risk profile, is offered when glaucoma progresses despite treatment with medication or laser.

Minimally invasive glaucoma surgical procedures involve implantation of devices such as the iStent. They have been proposed as a safer alternative to standard glaucoma surgeries in people with mild-to-moderate forms of open-angle glaucoma. The iStent creates a 'bypass' between the front chambers of the eye and its natural drainage pathway. This bypass increases the flow of fluids out of the eye, which may decrease IOP and the need to use glaucoma drops to control IOP.

What were the main results of this review?

We identified four RCTs that randomized participants to treatment with iStents in combination with cataract surgery (called phacoemulsification) or with phacoemulsification alone. Additionally, we identified two RCTs that randomized participants to treatment with iStents or to medical interventions. We also identified one RCT that randomized participants to treatment with one iStent, with two iStents, or with three iStents. The manufacturer of the iStent provided funding and sponsorship for all the RCTs in this review.

Based on low-quality evidence, we found that participants who received iStent in combination with cataract surgery were more likely to be drop-free and may have experienced a modest reduction in number of glaucoma drops used per day to control IOP in the medium term, compared with participants who underwent cataract surgery alone; however, there was no difference in average change from baseline in IOP between the two groups.

Due to substantial heterogeneity, we did not conduct an analysis of the two studies comparing treatment with iStent to medical therapy. Investigators of those two studies reported that no participants in the medical therapy group were drop-free at 12 months, compared to over 90% in the iStent treatment groups. Data suggested that treatment of people with two or with three iStents may have been more effective than treatment with one iStent in terms of IOP control.

None of the seven studies included in this review provided information on quality of life, and differences in complications or side effects between treatment groups were uncertain, given few reported events and varied effectiveness.

How up to date is the review?

We searched for studies published up to 17 August 2018.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. IStent in combination with phacoemulsification compared to phacoemulsification alone for open-angle glaucoma

iStent in combination with phacoemulsification compared to phacoemulsification alone for open-angle glaucoma

Patient or population: open-angle glaucoma
Setting: –
Intervention: iStent in combination with phacoemulsification
Comparison: phacoemulsification alone

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with phacoemulsification alone	Risk with iStent in combination with phacoemulsification				
Proportion of participants who were drop-free Follow-up: range 6 to ≤ 18 months	583 per 1000	804 per 1000 (688 to 950)	RR 1.38 (1.18 to 1.63)	239 (2 RCTs)	⊕⊖⊖⊖ **Very low**[a,b,c]	Estimate based on data from 2 trials.
Mean change in number of IOP-lowering drops from baseline Follow-up: range 6 to ≤ 18 months	The mean change in number of IOP-lowering drops from baseline ranged from –1.0 to 0.9 drops	MD 0.42 drops fewer (0.6 fewer to 0.23 fewer)	—	282 (2 RCTs)	⊕⊖⊖⊖ **Very low**[a,b,c]	In addition, Fernandez-Barrientos 2010 reported the change in number of IOP-lowering drops was 0 (SD 0) in the iStent in combination of phacoemulsification treatment group and 0.7 (SD 1) in the phacoemulsification alone group.
Mean change in IOP from baseline Follow-up: range 6 to ≤ 18 months	The mean change in IOP from baseline ranged from –8.5 to –1.6 mmHg	MD 1.24 mmHg lower (3.07 lower to 0.58 higher)	—	284 (3 RCTs)	⊕⊖⊖⊖ **Very low**[a,b,c,d]	—
Health-related quality of life	—		—	—	—	Not reported in any of the 4 studies.

Intraoperative complications	—	—	—	—	Samuelson 2011 reported that "[i]n an eye with intraoperative stent malposition, a second stent was implanted during the same surgery."
Postoperative complications	Based on available data, participants who were randomized to treatment with phacoemulsification in combination with iStent were less likely to experience elevated IOP (or IOP spikes) and loss of vision than those randomized to phacoemulsification alone.	—	334 (4 RCTs)	—	We did not conduct a meta-analysis of complications.
Secondary glaucoma surgery Follow-up: range 6 to ≤ 18 months	1 participant randomized to treatment with phacoemulsification in combination with iStent and 1 participant randomized to phacoemulsification alone underwent selective laser trabeculoplasty at 12 months.	—	290 (3 RCTs)	—	We did not conduct a meta-analysis of complications.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **IOP:** intraocular pressure; **MD:** mean difference; **RCT:** randomized controlled trial; **RR:** risk ratio; **SD:** standard deviation.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded one level for high or unclear risk of bias for blinding of outcome assessor.
[b]Downgraded one level for imprecision due to small sample size/wide confidence interval.
[c]Downgraded one level for publication bias due to potential for industry influences.
[d]Downgraded one level for heterogeneity (e.g. $I^2 > 70\%$) or inconsistency across trials.

Summary of findings 2. IStent (or iStent inject) compared to medical therapy for open-angle glaucoma

IStent (or iStent inject) compared to medical therapy for open-angle glaucoma

Patient or population: open-angle glaucoma
Setting: –
Intervention: iStent (or iStent inject)
Comparison: medical therapy

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with medical therapy	Risk with iStent (or iStent inject)				
Proportion of participants who were drop-free Follow-up: range 6 to ≤ 18 months	At 12 months, 0/138 participants randomized to medical therapy were drop-free at 12 months, while 141/148 (95%) participants randomized to treatment with iStent were drop-free at 12 months. We did not derive an RR because no events occurred in the control groups of either trial.		—	286 (2 RCTs)	⊕⊖⊖⊖ **Very low**[a,b,c]	In addition, Vold 2016 noted that 48/54 (88%) participants in the iStent treatment group were drop-free at 36 months.
Mean change in number of IOP-lowering drops from baseline	—	—	—	—	—	Not reported in either study.
Mean change in IOP from baseline Follow-up: range 6 to ≤ 18 months	The mean change in IOP from baseline was –11.6 mmHg	MD 0.6 mmHg lower (1.28 lower to 0.08 higher)	—	184 (1 RCT)	⊕⊖⊖⊖ **Very low**[a,b,c]	Vold 2016 did not report mean change in IOP but did provide mean IOP (without SD) at 6 months (14.2 mmHg), 18 months (13.5 mmHg), and 36 months (14.6 mmHg) in the iStent treatment groups; and at 6 months (13.8 mmHg), 18 months (14.6 mmHg), and 36 months (15.3 mmHg) in the medical therapy group.
Health-related quality of life	—		—	—	—	Not reported in either study.
Intraoperative complications	1 participant in the iStent treatment group experienced hyphema which resolved by day 1		—	101 (1 RCT)	—	We did not conduct a meta-analysis of complications.
Postoperative complications	Vold 2016 noted that best-corrected visual acuity was stable between both groups and did not report on any other postoperative complications. Fea 2014 reported that 1 participant in the iStent inject group experienced IOP decompensation with an elevated IOP of 48 mmHg.		—	286 (2 RCTs)	—	We did not conduct a meta-analysis of complications.
Secondary glaucoma surgery	Fea 2014 reported that 1 participant needed laser treatment to remove an apparent obstruction		—	286 (2 RCTs)	—	We did not conduct a meta-analysis of complications.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **IOP:** intraocular pressure; **MD:** mean difference; **RCT:** randomized controlled trial; **RR:** risk ratio; **SD:** standard deviation.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

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[a]Downgraded one level for imprecision due to small sample size/wide confidence interval.
[b]Downgraded one level for high or unclear risk of bias for blinding of outcome assessor.
[c]Downgraded one level for publication bias due to potential for industry influences.

BACKGROUND

Description of the condition

Glaucoma is a group of diseases characterized by clinical and histopathological manifestations of optic nerve damage that leads to irreversible vision loss (Allingham 2010). Glaucoma is the second leading cause of blindness, affecting approximately 60 million people worldwide (Quigley 2006). One systematic review estimated that the global prevalence of glaucoma in people between 40 and 80 years of age may increase to 76 million by 2020 and to 111.8 million by 2040 (Tham 2014). Open-angle glaucoma (OAG) is the most common type of glaucoma and accounts for approximately 74% of all cases (Quigley 2006). Women comprise 55% of OAG cases, and OAG disproportionately affects people of African ancestry and older adults (NEI 2015).

OAG is a progressive disease. In early mild-to-moderate stages, there are no symptoms (AAO 2015). Due to the 'silent' nature of OAG, people do not usually have any visual problems; there are optic nerve abnormalities consistent with glaucoma, but little to no aberrations in visual fields. In severe stages of glaucoma, people may notice vision loss or blind spots due to significant amounts of irreversible optic nerve damage (AAO 2015). Main signs of glaucoma include atrophied optic nerve and presence of an open angle, both of which can only be seen using specialized instruments.

Many people with OAG also experience elevated intraocular pressure (IOP); however, IOP is not a direct measure of structural or functional glaucomatous optic neuropathy and not all people with glaucoma present with elevated IOP (AAO 2015; Le 2016; Medeiros 2015). Nevertheless, because IOP is the only known modifiable risk factor, treatment for OAG has focused predominantly on lowering IOP (Li 2016; Quigley 2007).

Description of the intervention

Lowering IOP is achieved through medical, laser, and surgical interventions, typically implemented in a step-wise manner (AAO 2015; Le 2018a; NICE 2009). Since the early 2000s, a series of new treatment modalities, which the US Food and Drug Administration (FDA) refers to as "minimally invasive glaucoma surgical" (MIGS) devices, has emerged. MIGS are ab interno procedures that require minimal to no conjunctival manipulation or scleral dissection, which are readily combined with another intraocular procedure such as cataract extraction by phacoemulsification (cataract surgery). MIGS typically lower IOP to a more modest degree than traditional filtering surgeries (e.g. trabeculectomy or tube shunt implantation); however, MIGS may pose fewer risks than those more invasive surgeries (Caprioli 2015; Francis 2011; Spaeth 2015). While MIGS generally are not used as first-line therapy for glaucoma at this time, they may reduce the need for medication.

Examples of MIGS interventions include the iStent and iStent Inject, trabectome ab interno trabeculectomy, endoscopic cyclophotocoagulation (ECP), gonioscopy-assisted transluminal trabeculotomy (GATT), the Hydrus Microstent intracanalicular scaffold, the XEN Gel Stent, and the Innfocus Microshunt. Of these, the first four are currently FDA approved for use in the US; the others are being evaluated in clinical trials.

This Cochrane Review examined the iStent and iStent inject (Glaukos Corporation, Laguna Hills, CA, USA), the former of which was the first MIGS device to have received FDA approval, for people with mild-to-moderate OAG.

1. The iStent is a heparin-coated non-ferromagnetic titanium 'L-shaped' device, 1 mm in length with a head 0.3 mm in height facing the anterior chamber (Glaukos 2016). This MIGS device is preloaded into a single-use injector and then inserted ab interno through the trabecular meshwork under direct gonioscopic view (Manasses 2016). The iStent creates a permanent opening that directly connects the anterior chamber to Schlemm's canal.
2. The iStent inject is a second-generation 'mushroom-shaped' MIGS device, 360 µm in length with a conical head with maximum width of 230 µm. Like the iStent, the iStent inject is made of heparin-coated titanium but the conical head contains four evenly spaced outlets that allow fluid to pass from the anterior chamber into Schlemm's canal (Bahler 2012). The injector is preloaded with two iStent inject MIGS devices and is designed to deliver both stents, ab interno, into Schlemm's canal while entering the eye only once (Bahler 2012; Klamann 2015).

How the intervention might work

IOP increases when there is an imbalance between production and outflow of aqueous humor (a clear fluid that provides avascular ocular structures with nutrition). Aqueous humor drains through a complex network of cells and tissue (trabecular meshwork, Schlemm's canal, and collector channels) in an area known as the drainage angle (AAO 2015).

Given that the trabecular meshwork is the primary site of aqueous outflow and that resistance to aqueous humor outflow in this region largely determines IOP (Manasses 2016), bypassing the trabecular meshwork is a viable method to decrease IOP. Ab interno implantation of MIGS devices such as the iStent and iStent inject may increase outflow facility by providing direct access to Schlemm's canal and downstream collector channels via a permanent opening through trabecular meshwork (Francis 2011).

Why it is important to do this review

Most treatments for OAG rely primarily on lowering IOP (AAO 2015; AGIS 2000; EGS 2014), but they all have limitations. Many people with mild-to-moderate OAG elect to start with medical treatment (e.g. topical eye drops) as first-line therapy (AAO 2015; Li 2016; NICE 2009); commercially available eye drops have short durations of effect and adherence is poor (Friedman 2009; Okeke 2009). Conventional surgical procedures to bypass the trabecular meshwork and drainage angle, such as trabeculectomy and tube shunts or valves, are associated with variable frequencies of success and complications (Gedde 2012a; Gedde 2012b; Spaeth 2015). Trabeculectomies fail after about five years in approximately 50% of cases (Gedde 2012a; Gedde 2012b; Kirwan 2013; Lichter 2001). Laser trabeculoplasty (LTP) represents an intermediate intervention between drops and surgery, or can be used as an alternative first line to drops, but its efficacy has been noted to decrease over time and most people ultimately require repeat LTP or surgery (Leahy 2015; Patel 2015; Rolim de Moura 2007; Woo 2015).

MIGS procedures are becoming increasingly common, with their proponents claiming better safety profiles than other glaucoma surgical techniques (Brandao 2013; Larsen 2017). In this review,

we specifically examined the evidence for the effectiveness and safety of one type of MIGS device – the iStent and iStent inject – in people with mild-to-moderate OAG of any type. This review was undertaken as part of the Cochrane Eyes and Vision MIGS Consortium. The Consortium also reviewed other types of MIGS techniques and devices including the Trabectome (NeoMedix, Tustin, CA, USA), Hydrus Microstent (Ivantis, Irvine, CA, USA) (Otarola 2017), ECP (Endo Optiks, Waltham, MA, USA) (Tóth 2019), and XEN Glaucoma Implant (AqueSys Implant, Aliso Viejo, CA, USA) (King 2018).

OBJECTIVES

To assess the effectiveness and safety of ab interno trabecular bypass surgery with iStent (or iStent inject) for open-angle glaucoma in comparison to conventional medical, laser, or surgical treatment.

METHODS

Criteria for considering studies for this review

Types of studies

We included only randomized controlled trials (RCTs), prepared in any language, irrespective of their publication status.

Types of participants

We included studies of people with mild-to-moderate OAG of any type, including primary and secondary OAG. Primary OAG refers to glaucoma that develops due to an unknown cause; secondary OAG develops from a known cause, such as trauma to the eye or ocular inflammatory diseases. In the absence of a universally accepted definition for glaucoma, we permitted studies to use their own criteria to define OAG; however, we excluded studies of participants with angle-closure glaucoma (where increased IOP occurs because abnormal iris anatomy obstructs aqueous flow to the drainage angle). In addition, we allowed studies that included participants with ocular hypertension (OHT), normal tension glaucoma, or possible OAG (i.e. suspected).

Types of interventions

We included studies that compared iStent or iStent inject (Glaukos Corporation, Laguna Hills, CA, USA) to any of the following:

1. laser treatment (selective LTP or argon LTP);
2. other MIGS procedures/techniques;
3. conventional glaucoma surgery (trabeculectomy);
4. medical therapy; or
5. in combination with phacoemulsification compared with phacoemulsification alone. iStent devices are approved in people undergoing phacoemulsification.

Additionally, we conducted stratified analyses based on iStent procedures (e.g. iStent versus iStent inject).

Types of outcome measures

We did not use reporting of particular outcomes as a criterion for including a trial into our systematic review. We, as with other review teams in the Consortium, adapted primary and secondary outcomes from a Cochrane systematic review prepared by Hu and colleagues (Hu 2016).

We evaluated each outcome at a time point in the six to 18 months (medium-term) time window, in addition to less than six months (short-term), over 18 but less than or equal to 36 months (long-term), and over 36 months time windows. We recognized that our primary outcome may not be relevant in RCTs that randomized participants to medical therapy in lieu of an iStent procedure.

Primary outcomes

1. Proportion of participants who were drop-free (i.e. not using eye drops) at a time point in each of the time windows.

Secondary outcomes

1. Mean change in number of IOP-lowering drops taken per day from baseline to a time point in each of the time windows.
2. Mean change in IOP, measured using Goldmann applanation tonometry, from baseline to a time point in each of the time windows.
3. Any health-related quality of life measures, measured as mean change from baseline or proportion meeting a threshold at a time point in each of the time windows, as defined by the investigators of the included trials.

Adverse outcomes

1. Proportions of participants experiencing intra- and postoperative complications at a time point in each of the time windows, including but not restricted to the following:
   a. loss of visual acuity of more than 2 Snellen lines, or more than 0.3 logMAR, according to the method of recording visual acuity; or loss of light perception;
   b. bleeding, as recorded by the investigators;
   c. endophthalmitis, as recorded by the investigators;
   d. IOP spikes, defined as postoperative rise in IOP, measured using Goldmann applanation tonometry, of more than 10 mmHg compared to the previous assessment, including during the first postoperative month;
   e. secondary glaucoma surgery, including laser, as recorded by the investigators of the included trials.

Search methods for identification of studies

Electronic searches

The Cochrane Eyes and Vision Information Specialist searched the following electronic databases for RCTs and controlled clinical trials. We used no restrictions on language or year of publication.

1. Cochrane Central Register of Controlled Trials (CENTRAL; 2018, Issue 7; which contains the Cochrane Eyes and Vision Trials Register) in the Cochrane Library (searched 17 August 2018; Appendix 1).
2. MEDLINE Ovid (1946 to 17 August 2018; Appendix 2).
3. Embase Ovid (1980 to 17 August 2018; Appendix 3).
4. ISRCTN registry (www.isrctn.com/editAdvancedSearch; searched 17 August 2018; Appendix 4).
5. US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov; searched 17 August 2018; Appendix 5).
6. World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp; searched 17 August 2018; Appendix 6).

7. US FDA website (www.fda.gov; searched 17 August 2018; Appendix 7).

Searching other resources

We searched the reference lists of included studies for possible studies and the website of the manufacturer for information regarding forthcoming trials (Glaukos 2016).

Data collection and analysis

Selection of studies

Two review authors (JL and TL) worked independently to screen titles and abstracts of all records identified by the search using web-based review management software (Covidence 2015). We removed duplicates from the search results. The review authors classified each record as either relevant (a 'Yes' vote) or not relevant (a 'No' vote) for full-text review. The two review authors independently assessed the full-text copies of all titles and abstracts that they identified as relevant to determine if the reports met the inclusion criteria (an 'Include' vote) or not (an 'Exclude' vote). We did not need to contact the trial authors of any record to clarify details necessary to make a complete assessment of the eligibility. We documented reasons for exclusion for each study assessed as not eligible after review of the full-text articles. We resolved all discrepancies between review authors by discussion at each stage of the screening process. We then linked multiple reports originating from the same trial.

Data extraction and management

Two review authors (JL and LW) independently extracted data using a web-based electronic data collection form in SRDR (srdr.ahrq.gov/). We extracted the information as described in Appendix 8, including: study setting, countries where recruitment took place, sample size, study duration and follow-up time, study design, analysis choice, sources of funding, and potential conflicts of interests; characteristics of the participants (e.g. inclusion/exclusion criteria), underlying disease conditions, and medical history (including IOP at baseline, number of glaucoma medications at baseline, visual acuity, and other vision-related characteristics); interventions (e.g. iStent or iStent inject) and comparators (e.g. type of laser, drugs, surgery, duration, and timing); outcomes (e.g. domain, specific measurement, specific metric, method of aggregation, and time frame); and quantitative results.

The review authors compared the extracted data and resolved discrepancies by discussion. One review author (JL) completed data entry into Review Manager 5 (Review Manager 2014), and a second review author (LW) verified the data entered.

Assessment of risk of bias in included studies

Two review authors (JL and LW) independently assessed the risk of bias in included studies, following guidance described in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2017). Specific items for consideration included random sequence generation and allocation concealment (selection bias), masking of study personnel (performance bias), masking of outcome assessors (detection bias) for number of IOP-lowering drops used and for IOP measurement, missing data and intention-to-treat analysis (attrition bias), and selective outcome reporting (reporting bias).

We assigned each item as having low risk, high risk, or, if the information provided was insufficient to make an assessment, unclear risk. We documented reasons for those assessments and resolved discrepancies through discussion. We presented the overall assessments as the 'Risk of bias' summary figure (Higgins 2017).

Measures of treatment effect

We used mean difference (MD) as the measure of effect for all continuous outcomes, with 95% confidence intervals (CI). We used risk ratio (RR) with 95% CIs as the measure of effect for all binary and categorical outcomes.

Unit of analysis issues

We assessed whether the included trials included one or both eyes from each participant and whether the trial investigators randomized (and analyzed) at the participant-level or at the eye-level. When both eyes were randomized to different treatments, we planned to extract the results that had accounted for the correlation.

Dealing with missing data

Where data on included studies were unclear or missing, we planned to write to the authors and analyze the data using the best information available if we received no response within two weeks. We planned to consider multiple imputation or other imputation approaches for handling missing data if needed. If the quality of the available data prevented any meaningful analysis, we planned to omit the study from quantitative analyses and note this decision in the discussion.

Assessment of heterogeneity

We assessed clinical and methodological heterogeneity by examining participant characteristics, MIGS techniques and devices, and outcomes, taking into consideration potential risk of bias. We assessed forest plots and examined the I^2 statistic and its CI for statistical heterogeneity. Similar to other protocols on MIGS procedures, we considered an I^2 statistic greater than 50% as indicative of substantial heterogeneity, suggesting that a meta-analysis may not be appropriate. However, if all estimates were in the same direction, we pursued a meta-analysis despite substantial statistical heterogeneity, and we interpreted the findings taking into consideration the heterogeneity.

Assessment of reporting biases

We planned to assess small-study effects using funnel plots if there were more than 10 trials for each meta-analysis. We assessed selective reporting as part of the 'Risk of bias' assessment, for example, examining differences between trial registration, protocol, and publication.

Data synthesis

We followed Chapter 9 of the*Cochrane Handbook for Systematic Reviews of Interventions* for data synthesis and analysis (Deeks 2017). We first provided a descriptive, qualitative synthesis of studies and their results. We used fixed-effect models for all meta-analyses.

Subgroup analysis and investigation of heterogeneity

We planned to conduct a subgroup analysis by type of iStent (iStent or iStent inject).

Sensitivity analysis

We planned to conduct additional sensitivity analyses to determine the impact of any post hoc decisions made during the review process.

'Summary of findings' tables

We prepared 'Summary of findings' tables using the GRADE approach to assess the certainty of the evidence (GRADEpro GDT 2015). We planned to include following outcomes in the summary.

1. Proportion of participants who were drop-free (not using eye drops) at six to 18 months.
2. Mean change in number of IOP-lowering drops taken per day from baseline to six to 18 months
3. Mean change in IOP, measured using Goldmann applanation tonometry, from baseline to six to 18 months.
4. Health-related quality of life at six to 18 months.
5. Intraoperative complications at six to 18 months.
6. Postoperative complications up to six to 18 months.
7. Secondary glaucoma surgery, including laser, as recorded by the investigators of the included trials between baseline and six to 18 months.

We summarized findings from two comparison groups: in combination with phacoemulsification compared with phacoemulsification alone and iStent compared to medical therapy. We downgraded the level of certainty of the evidence if the contributing studies were at high or unclear risk of bias for masking of outcome assessors (one level), provided inconsistent estimates (one level) or imprecise estimates (one level) due to small sample size or wide CIs, or may have been subject to publication bias (one level). Guyatt 2011 noted that inclination to downgrade for publication bias should increase when evidence comes from small studies which are "industry sponsored or likely to be industry sponsored (or if the investigators share another conflict of interest)." We also presented results of one trial which compared one iStent with two iStents with three iStents, but did not assess the certainty of the evidence or present a 'Summary of findings' table for this single trial.

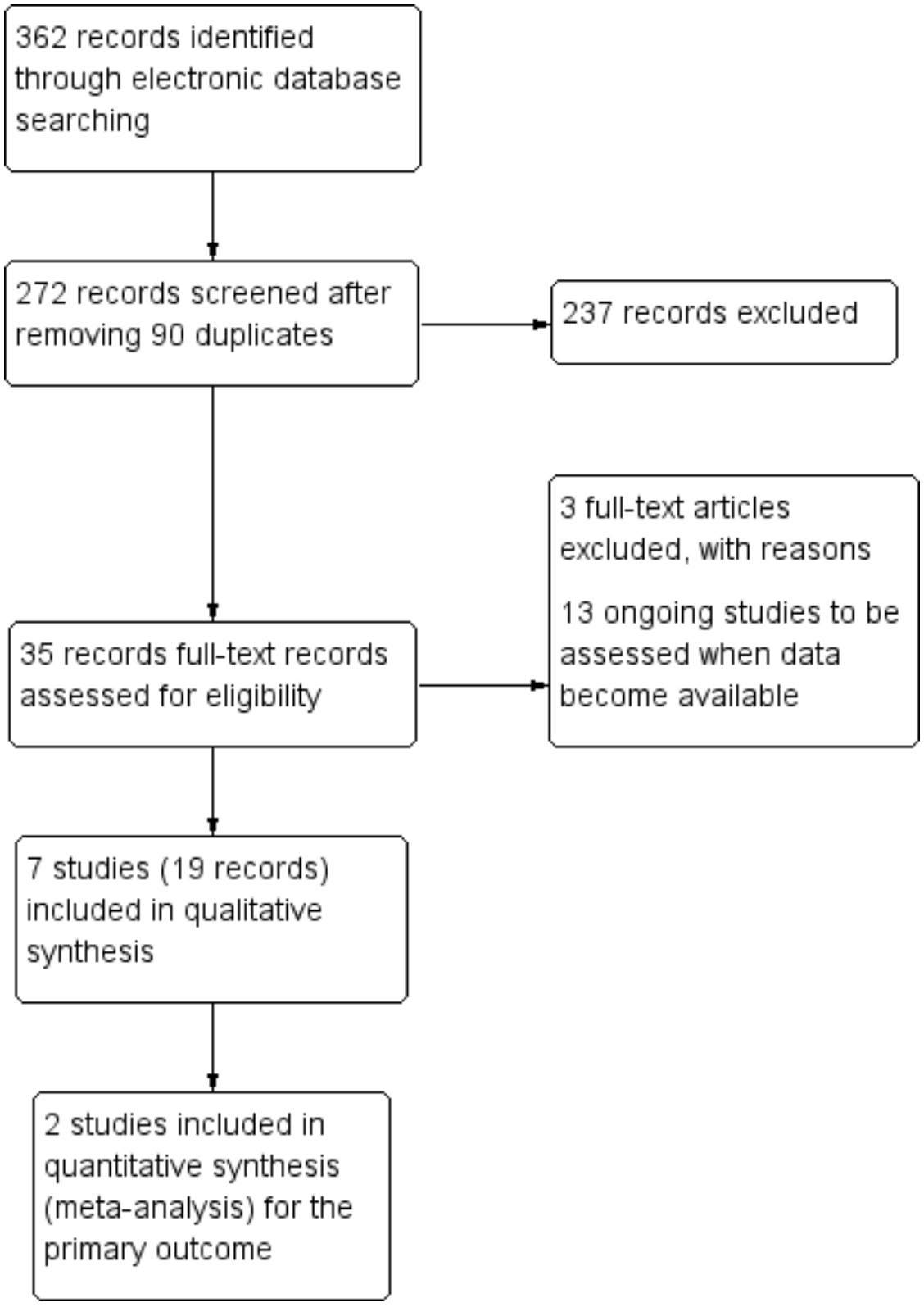
RESULTS

Description of studies

Results of the search

The electronic search yielded 362 records (Figure 1). After removal of 90 duplicates, we screened the remaining 272 records and excluded a further 237 records based on information in the title and abstract. We obtained full-text reports of 35 records for further investigation. We included 19 reports of seven studies (see Characteristics of included studies table) and excluded three reports of three studies (see Characteristics of excluded studies table). We identified 13 ongoing studies that potentially met the inclusion criteria, these studies will be assessed when data become available (see Characteristics of ongoing studies table for further details).

Figure 1. Study flow diagram.



Included studies

Type of studies

We included seven RCTs (Fea 2010; Fea 2014; Fernandez-Barrientos 2010; Katz 2015; NCT00721968; Samuelson 2011; Vold 2016). Most RCTs were multi-center trials in which participants were recruited from Armenia (two RCTs); Italy (one RCT); Spain (one RCT); the US (two RCTs); or the previous four countries in addition to Germany and the UK (one RCT) (see Characteristics of included studies table). Six trials began enrollment of participants prior to 2010, and the maximal planned length of follow-up ranged from one to five years (Fea 2010; Fea 2014; Fernandez-Barrientos 2010; Katz 2015; NCT00721968; Samuelson 2011). All seven RCTs reported having received support – including financial, non-study financial, or non-financial support (e.g. study devices, editorial assistance, or payment of article processing charges) – from the Glaukos Corporation (Laguna Hills, CA, USA), manufacturer of the iStent and iStent inject.

Type of participants

The seven RCTs enrolled 764 participants (765 eyes; range per study: 33 to 239 participants). Most participants were white, female sex (417/764 (55%)), and older age (range: 49 to 89 years). The diagnosis of participants varied between studies: some included people with OHT, pseudoexfoliative glaucoma (PXG), or pigmentary glaucoma (PG) in addition to OAG. Most excluded participants with prior incisional glaucoma surgery, and four trials included only participants with OAG in need of cataract surgery (Fea 2010; Fernandez-Barrientos 2010; NCT00721968; Samuelson 2011). Four trials reported that participants were washed out of current glaucoma medication (Fea 2014; Fernandez-Barrientos 2010; Katz 2015; Samuelson 2011); one trial recruited only treatment-naïve participants (Vold 2016). Table 1 provides a synopsis of the trial-level eligibility criteria.

Type of interventions

Four RCTs compared treatment with iStent in combination with phacoemulsification to phacoemulsification alone; specifically: Fea 2010, NCT00721968, and Samuelson 2011 compared the iStent combined with phacoemulsification to phacoemulsification alone, and Fernandez-Barrientos 2010 compared two iStents combined with phacoemulsification to phacoemulsification alone.

The remaining three RCTs did not use phacoemulsification as a concomitant intervention: Vold 2016 compared two iStents with topical travoprost (Travatan; Alcon, Fort Worth, TX, USA); Fea 2014 compared the iStent inject with fixed combination of latanoprost/timolol (Xalacom; Pfizer, New York, NY, USA); and Katz 2015 compared one iStent with two iStents and with three iStents.

Type of outcomes

Five RCTs reported our primary outcome (proportion of participants who were drop-free at two years) (Fea 2010; Fea 2014; Katz 2015; Samuelson 2011; Vold 2016). The two RCTs that did not report on our primary outcome (Fernandez-Barrientos 2010; NCT00721968), along with Samuelson 2011, provided data on the mean change in number of IOP-lowering drops. Four RCTs reported mean change in IOP postwashout of any glaucoma medications (Fernandez-Barrientos 2010; Katz 2015; NCT00721968; Samuelson 2011). Proportions of participants experiencing complications were reported variably among the seven RCTs. No RCTs reported quality of life.

Three RCTS described calculating sample sizes, based on the ability to detect a 19.5% difference in proportion of participants with IOP 21 mmHg or less at one year (Samuelson 2011); a difference in IOP of approximately 3 mmHg at 15 months (Fea 2010); or a 0.3 µL/minute/mmHg difference in the outflow facility at one year (Fernandez-Barrientos 2010).

We summarized clinically important and surgery-related adverse events of interest in Table 2.

Excluded studies

We excluded two studies that were not RCTs. Bacharach 2014 was a subsequent observational extension of Samuelson 2011, where a non-randomized population of 46 participants were added to the treatment arm. Vlasov 2017 was a retrospective case series review of one versus two iStent implantations in combination with phacoemulsification. We also excluded one study which was withdrawn before enrolling the first participant (NCT03274323).

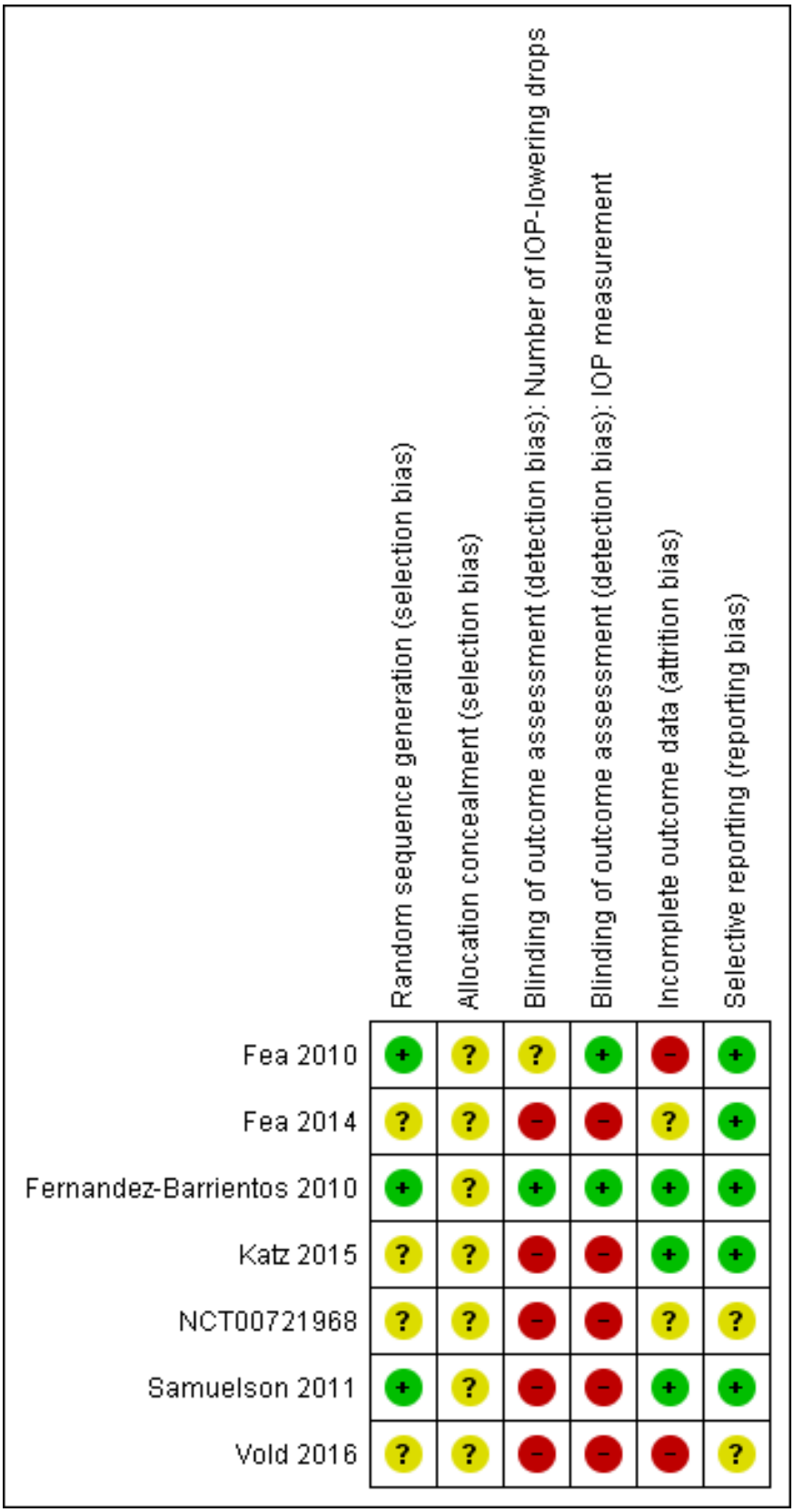
Ongoing studies

We identified 13 ongoing studies awaiting classification. All 13 are described as RCTs and are recruiting participants from Armenia, Australia, Germany, Japan, Spain, Turkey, and the US. Participants are randomized to treatment with iStent compared to treatment with no iStent (e.g. phacoemulsification alone), to medical therapy (e.g. latanoprost and timolol), to different number of iStents implanted (e.g. one versus two stents), to SLT laser treatment, to the Hydrus Microstent (see Characteristics of ongoing studies table). The studies are funded mostly by manufacturers of the devices.

Risk of bias in included studies

We summarized the risk of bias in the included trials in Figure 2.

Figure 2. Risk of bias summary: review authors' judgments about each risk of bias item for each included study.



Allocation

Random sequence generation

Three RCTs reported how investigators generated the random allocation sequence: Fea 2010, Fernandez-Barrientos 2010, and Samuelson 2011 used a computer-based random generator, a method that we considered to be at low risk of bias. We assessed the remaining four RCTs, which did not report the method of generating the allocation sequence, at unclear risk of bias.

Allocation concealment

No studies described the method used to conceal the allocation sequence. We assessed all seven trials at unclear risk of bias.

Blinding

One RCT reported that the same examiner, "who was masked to the type of surgery performed" performed all postoperative evaluations (Fernandez-Barrientos 2010). Accordingly, we assessed the risk of bias in blinding of outcome assessments as low for both 'number of IOP-lowering drops' and 'IOP measurement' outcome domains. Although Fea 2010 noted that "staff members who measured IOP throughout the study" were masked (low risk of bias), it was unclear whether this same staff member also assessed the number of IOP-lowering drops that participants were taking per day (unclear risk of bias). We assessed the remaining five trials, which investigators described as "not masked" (Fea 2014) or "open-label" (Katz 2015; NCT00721968; Samuelson 2011; Vold 2016), at high risk of detection bias.

Incomplete outcome data

We considered three RCTs at low risk of bias for incomplete outcome data because there were no missing data on outcomes of our review (Fernandez-Barrientos 2010; Katz 2015; Samuelson 2011). We assessed two RCTs at high risk of bias for incomplete outcome data: Fea 2010 excluded 3/36 participants (all randomized to the phacoemulsification alone group) from the final analysis and Vold 2016 conducted an available-case analysis of 73/101 (72%) participants at 36 months. We assessed the remaining two RCTs at unclear risk of bias because the full publication is not yet available (NCT00721968), or the completeness of outcome data varied by time points reported (Fea 2014).

Selective reporting

We considered the risk of selective reporting to be low for five RCTs because outcomes described in the results matched those specified in methods section and in the trial registrations (Fea 2010; Fea 2014; Fernandez-Barrientos 2010; Katz 2015; Samuelson 2011). We considered the risk of selective reporting was unclear for NCT00721968, because the full publication of trial results is not yet available; and for Vold 2016, because of differences between the primary outcomes specified on ClinicalTrials.gov ("change from screening in mean diurnal IOP (mm Hg) at the Month 12 visit") and in the published trial report (mean IOP up to 36 months; "diurnal measurements of IOP were not performed").

Effects of interventions

See: **Summary of findings for the main comparison** IStent in combination with phacoemulsification compared to phacoemulsification alone for open-angle glaucoma; **Summary of findings 2** IStent (or iStent inject) compared to medical therapy for open-angle glaucoma

Based on the data available, the comparisons that we could make at time of writing this review were: 1. iStent in combination with phacoemulsification versus phacoemulsification alone and 2. iStent (or iStent inject) versus medical therapy. We also summarized findings from one RCT that compared one iStent with two iStents with three iStents. We presented our analyses by comparison, outcome, and duration of follow-up in the order described.

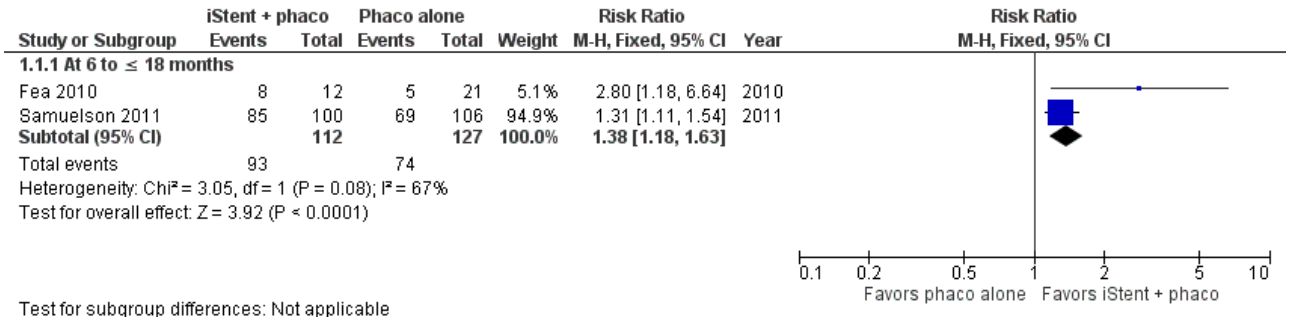
Comparison 1: iStent in combination with phacoemulsification versus phacoemulsification alone

Four RCTs, which randomized 353 participants with OAG in need of cataract surgery, compared iStent in combination with phacoemulsification versus phacoemulsification alone. Three RCTs implanted one iStent (Fea 2010; NCT00721968; Samuelson 2011); one RCT implanted two iStents (Fernandez-Barrientos 2010).

Proportion of participants who were drop-free

Two RCTs reported proportion of participants who were drop-free in the medium-term (Figure 3): Fea 2010 at 15 months (RR 2.80, 95% CI 1.18 to 6.64) and Samuelson 2011 at 12 months (RR 1.31, 95% CI 1.11 to 1.54). Although estimates from both studies were consistent in favoring treatment with one iStent in combination with phacoemulsification over phacoemulsification alone, we observed substantial statistical heterogeneity in the meta-analytical estimate (RR 1.38, 95% CI 1.18 to 1.63; $I^2 = 67\%$). We graded the certainty of evidence as very low, downgrading for risk of bias (one level), imprecision (one level), and potential publication bias (one level).

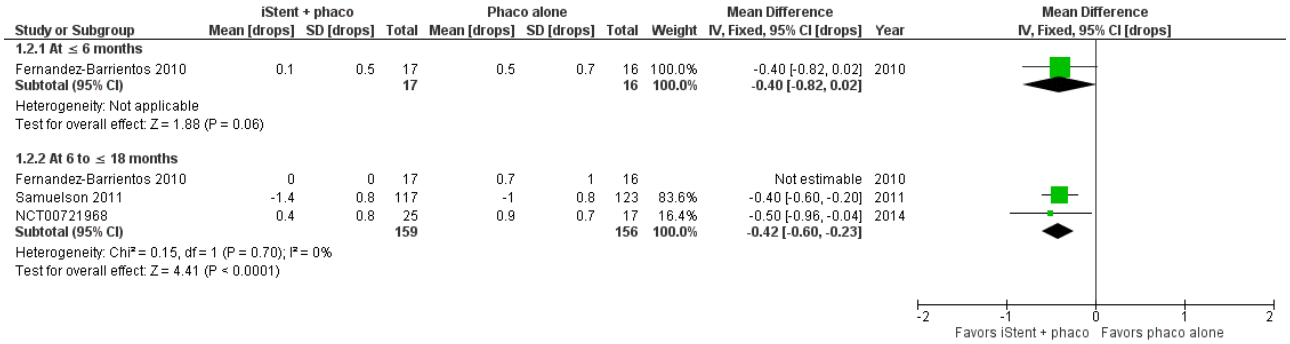
Figure 3. Forest plot of comparison: 1 iStent in combination with phacoemulsification versus phacoemulsification alone, outcome: 1.1 Proportion of participants who were drop-free.



Mean change in number of intraocular pressure-lowering drops

Samuelson 2011 observed a greater reduction from baseline in the number of IOP-lowering drops in the iStent in combination with phacoemulsification group than the phacoemulsification alone group at 12 months (MD −0.40 drops, 95% CI −0.60 to −0.20). NCT00721968 and Fernandez-Barrientos 2010 reported the mean number (rather than mean change from baseline) of IOP-lowering drops in each group at medium-term (Figure 4). Overall, iStent in combination with phacoemulsification reduced the number of IOP-lowering drops compared with phacoemulsification alone at medium term (MD −0.42, 95% CI −0.60 to −0.23; I^2 = 0%). Additionally, Fernandez-Barrientos 2010 found no statistically significant difference between treatment iStent in combination with phacoemulsification and phacoemulsification alone in the short-term (MD −0.40, 95% CI −0.82 to 0.02 at 6 months). We graded the certainty of evidence as very low for this outcome, downgrading for risk of bias (one level), imprecision (one level), and potential publication bias (one level).

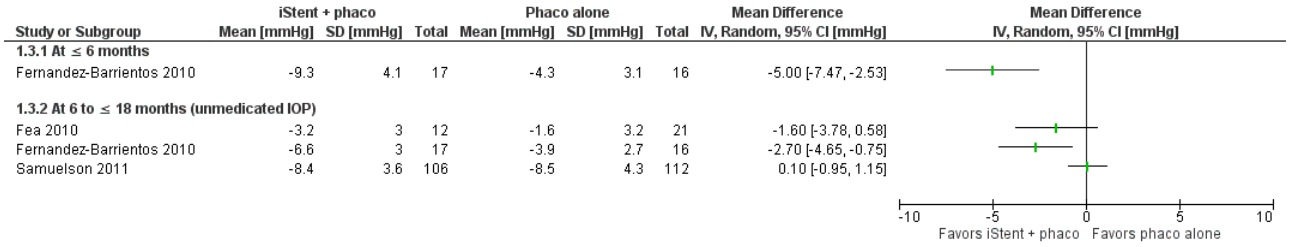
Figure 4. Forest plot of comparison: 1 iStent in combination with phacoemulsification versus phacoemulsification alone, outcome: 1.2 Mean change in number of intraocular pressure (IOP)-lowering drops taken per day from baseline.



Mean change in intraocular pressure

Three RCTs reported mean change in IOP at medium-term (Figure 5): Fea 2010 provided data at 15 months (MD −1.60, 95% CI −3.78 to 0.58); Fernandez-Barrientos 2010 at 12 months (MD −2.70, 95% CI −4.65 to −0.75); and Samuelson 2011 at 12 months (MD 0.10, 95% CI −0.95 to 1.15). We observed substantial statistical heterogeneity (I^2 = 71%) and did not conduct a meta-analysis; instead, we present the point estimates in a forest plot (Figure 5). We graded the certainty of evidence as very low, downgrading for risk of bias (one level), imprecision (one level), inconsistency (one level) and potential publication bias (one level).

Figure 5. Forest plot of comparison: 1 iStent in combination with phacoemulsification versus phacoemulsification alone, outcome: 1.3 Mean change in IOP.



Of note, Samuelson 2011, in which one iStent was implanted at the time of phacoemulsification in each study eye, reported that although mean reduction in IOP appeared similar in both groups at 12 months, "a substantially higher level of medications was used in the control [phacoemulsification only] group to maintain this similar IOP level." Additionally, at 24 months, the investigators of this RCT observed that mean IOP in the one iStent treatment group was 8.4 mmHg lower than baseline IOP, compared to 7.5 mmHg in the phacoemulsification alone group (Samuelson 2011); no standard deviations (SD) were provided and therefore we could not derive any between-group estimates.

Health-related quality of life

No trials reported health-related quality of life.

Intra- and postoperative complications from baseline

Samuelson 2011 reported one intraoperative complication where "[i]n an eye with intraoperative stent malposition, a second stent was implanted during the same surgery."

The reporting of postoperative complications varied by RCT (Table 3).

1. In Samuelson 2011, one participant in each treatment group experienced best-corrected visual acuity (BCVA) loss

and two participants in each treatment group experienced "subconjunctival hemorrhage" at 12 months. Two participants in the iStent treatment group experienced and elevation of IOP requiring treatment at 12 months compared to one participant in the phacoemulsification alone group. Data comparing number of participants who needed secondary surgical interventions at 24 months in the iStent in combination with phacoemulsification group versus the phacoemulsification groups available for a subset "safety population" that excluded six participants who were terminated from the study before receiving surgery of any type. In this population, one participant treated with phacoemulsification in combination with iStent underwent a secondary glaucoma surgical intervention (trabeculoplasty).

2. In NCT00721968, participants in the iStent treatment group were less likely to experience IOP spikes at 12 months (RR 0.21, 95% CI 0.07 to 0.67).
3. In Fernandez-Barrientos 2010, one participant randomized to phacoemulsification underwent selective LTP at 12 months to manage their glaucoma.
4. In Fea 2010, none of the 24 participants (10 randomized to iStent in combination with phacoemulsification and 14 randomized to phacoemulsification alone) still under follow-up at 48 months needed secondary glaucoma surgery.

Comparison 2: iStent (or iStent inject) versus medical therapy

Two RCTs, which randomized 293 participants with OAG, compared treatment with either two iStents (Vold 2016) or the iStent inject (Fea 2014) with medical therapy. Medical therapy consisted of either a fixed combination of latanoprost/timolol (Fea 2014) or topical travoprost (Vold 2016). All participants in Fea 2014 were using one IOP-lowering medication at recruitment and, "in the opinion of the investigator, required additional IOP lowering." All participants enrolled in Vold 2016 were newly diagnosed and had not "undergone prior treatment of any kind" for their glaucoma. Because the patient population, intervention, and comparison were clinically heterogenous between these two RCTs, we did not conduct a meta-analysis for any outcomes.

Proportion of participants who were drop-free

Both RCTs reported proportion of participants who were drop-free in the medium-term. As one would expect based on study design, no participants who were randomized to medical therapy in either RCTs were drop-free at 12 months, compared with 96% (90/94; Fea 2014) and 94% (51/54; Vold 2016) of participants in the iStent treatment groups. Additionally, Vold 2016 observed that at 36 months, no participants in the medical therapy group were drop-free compared to 88% (48/54) of participants in the iStent treatment group. We did not derive an RR because no events occurred in the control group. We graded the certainty of evidence as very low, downgrading for risk of bias (one level), imprecision (one level), and potential publication bias (one level).

Mean change in number of intraocular pressure-lowering drops

Vold 2016 specifically reported medications required over and above the travoprost used as a study intervention, while Fea 2014 reported total number of medications required, regardless of response to medical therapy. Thus, neither Fea 2014 nor Vold 2016 provided mean change in number of IOP-lowering drops that could be analyzed for this review.

Mean change in intraocular pressure

Fea 2014 reported the mean change in IOP in the short-term (MD 0.10, 95% CI −0.72 to 0.92, at 6 months) and medium-term (MD −0.60, 95% CI −1.28 to 0.08, at 12 months), comparing iStent inject to medical therapy. Vold 2016 did not report mean change in IOP but provided mean IOP (without SD) at six months (14.2 mmHg in the iStent group versus 13.8 mmHg in the medical therapy group), 18 months (13.5 mmHg in the iStent group versus 14.6 mmHg in the medical therapy group), and 36 months (14.6 mmHg in the iStent group versus 15.3 mmHg in the medical therapy group). We graded the certainty of evidence as very low, downgrading for risk of bias (one level), imprecision (one level), and potential publication bias (one level).

Health-related quality of life

No studies reported health-related quality of life.

Intra- and postoperative complications from baseline

The reporting of intraoperative and postoperative complications varied by RCT.

1. Vold 2016 observed one participant with hyphema that resolved by day one and another participant with a small iridodialysis. The investigators also noted that six participants (five in the iStent treatment group and one in the medical therapy group) underwent cataract surgery at 36 months, but they did not report on need for secondary glaucoma surgery.
2. Fea 2014 reported one participant in the iStent inject treatment group who experienced "IOP decompensation with an elevated IOP (48 mmHg)" that resolved after treatment with medication; and one participant, also in the iStent inject treatment group, who required laser treatment to remove an apparent obstruction.

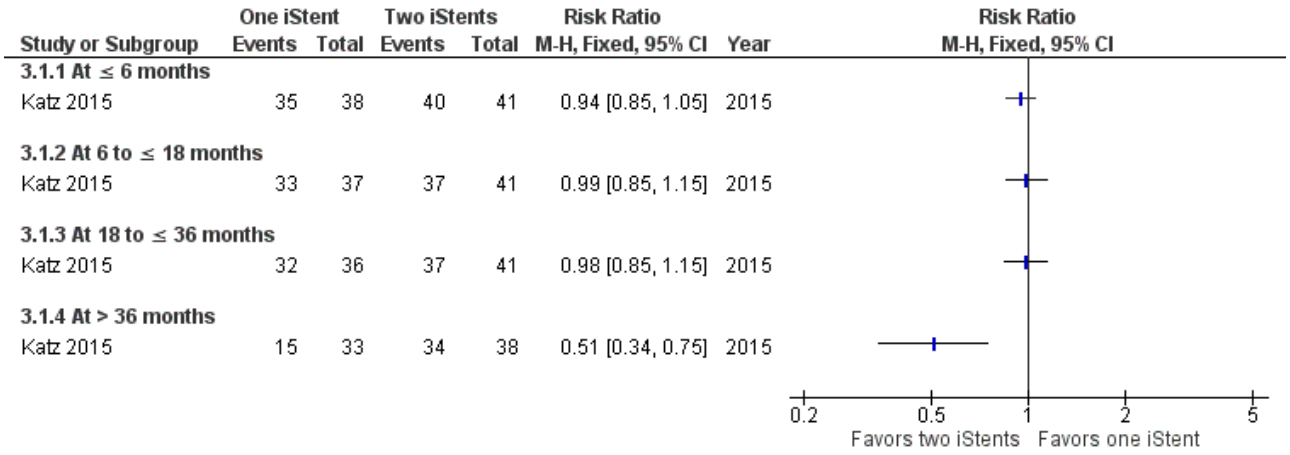
Additional comparison: one iStent versus two iStents versus three iStents

One three-arm RCT randomized 119 participants with OAG to treatment with one iStent, two iStents, or three iStents (Katz 2015). The investigators recruited participants from a single center in Armenia and followed them for five years. Results up to 42 months were available.

Proportion of participants who were drop-free

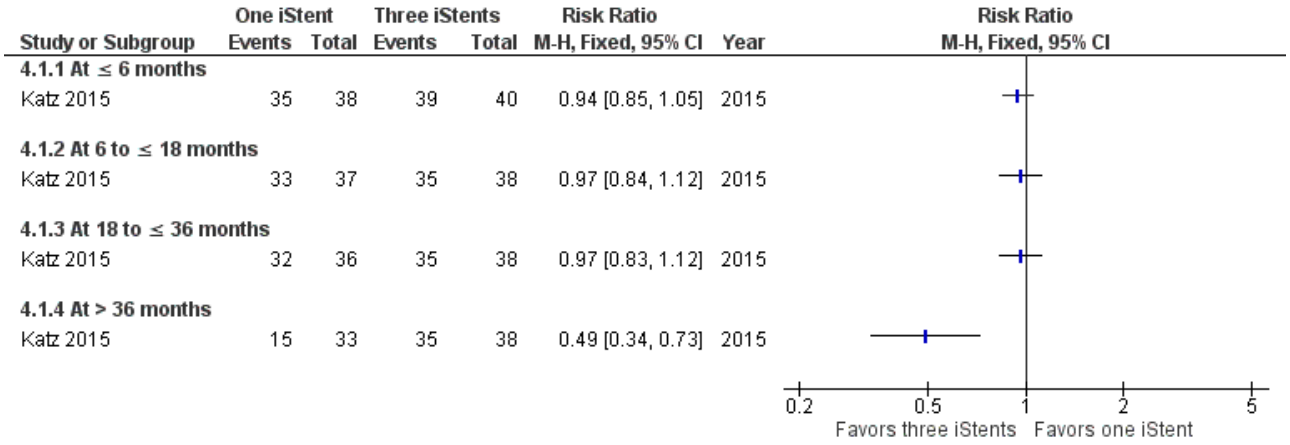
Comparing treatment with one iStent to treatment with two iStents, there was no difference in terms of participants who were drop-free at time points in the short-term (RR 0.94, 95% CI 0.85 to 1.05), medium-term (RR 0.99, 95% CI 0.85 to 1.15), and long-term (RR 0.98, 95% CI 0.85 to 1.15) (Figure 6). However, at more than 36 months, participants who were randomized to treatment with one iStent were less likely to be drop-free than those to treatment with two iStents (RR 0.51, 95% CI 0.34 to 0.75, at 42 months).

Figure 6. Forest plot of comparison: 3 One iStent (without phacoemulsification) versus two iStents (without phacoemulsification), outcome: 3.1 Proportion of participants who were drop-free.



Comparing treatment with one iStent to treatment with three iStents, there was also no difference in terms of participants who were drop-free at time points in the short-term (RR 0.94, 95% CI 0.85 to 1.05), medium-term (RR 0.97, 95% CI 0.84 to 1.12), and long-term (RR 0.97, 95% CI 0.83 to 1.12) (Figure 7). At more than 36 months, participants who were randomized to treatment with one iStent were less likely to be drop-free than those to treatment with three iStents (RR 0.49, 95% CI 0.34 to 0.73, at 42 months).

Figure 7. Forest plot of comparison: 4 One iStent (without phacoemulsification) versus three iStents (without phacoemulsification), outcome: 4.1 Proportion of participants who were drop-free.



Mean change in number of intraocular pressure-lowering drops

Katz 2015 did not report the mean change in number of IOP-lowering drops; however, the investigators noted that one participant in the two-iStent treatment group was prescribed two medications at 18 months. The remaining 13 participants who were using drops at 18 months were on one medication to control their IOP.

Mean change in intraocular pressures

Katz 2015 reported the mean change in IOP at 18 months as –3.94 mmHg in the one-iStent, –5.99 mmHg in the two-iStent, and –8.19 mmHg in the three-iStent treatment groups. No SD were reported; however, investigators provided mean IOP at six, 18, and 42 months with SDs. The investigators reported a statistically significant difference in mean IOP at 18 months, comparing treatment with one iStent to treatment with two iStents (MD 1.80 mmHg, 95% CI 1.17 to 2.43) and to treatment with three iStents (MD 3.50 mmHg, 95% CI 2.88 to 4.12), and no difference in mean IOP comparing treatment with one iStent to treatment with two iStents or to treatment with three iStents at six and 42 months

Health-related quality of life

Katz 2015 did not report health-related quality of life.

Intra- and postoperative complications from baseline

Katz 2015 noted that "no complications occurred intraoperatively or perioperatively, including no hypotony, choroidal effusion, hypema, nor iridodialysis." By 42 months, eight (21%) participants in the one-iStent, five (12%) participants in the two-iStent, and seven (18%) participants in three-iStent treatment groups had BCVA loss of 1 line or more due to cataract progression. Of these, five participants in the one-iStent, two participants in the two-

iStent, and three participants in the three-iStent treatment groups underwent cataract surgery by 42 months.

DISCUSSION

Summary of main results

We identified seven RCTs that compared treatment of people with the iStent (or iStent inject) to treatment with phacoemulsification alone, medical therapy, or different numbers of iStents. We summarized our findings after reviewing the available evidence in the 'Summary of findings' tables for the main comparison section (Summary of findings for the main comparison; Summary of findings 2).

There was considerable variability among the trials with respect to interventions evaluated, outcomes reported, and length of participant follow-up. The certainty of the evidence was very low.

1. In comparison 1, we examined four RCTs comparing treatment with iStent in combination with phacoemulsification to phacoemulsification alone. Data from two trials suggest that participants randomized to iStent were 1.38 times more likely to be drop-free between six and 18 months postsurgery. However, we observed uncertainty in this estimate (95% CI 1.18 to 1.63) and substantial statistical heterogeneity (I^2 = 67%).
2. In comparison 2, we examined RCTs comparing treatment with iStent (without phacoemulsification) to medical therapy. We determined the two studies in this comparison to be clinically and methodologically heterogeneous and did not conduct a meta-analysis. In both studies, at 12 months, no participants in the medical therapy groups were drop-free, while over 90% of participants in the iStent groups were drop-free.
3. Additionally, we found one RCT that compared participants randomized to treatment with one iStent to treatment with two iStents, and to treatment with three iStents. About 53% of participants in the one iStent treatment group were drop-free at 42 months compared to over 90% of participants in the two-iStent treatment group (RR 0.51, 95% CI 0.34 to 0.75) and three-iStent treatment group (RR 0.49, 95% CI 0.34 to 0.73).

All trials that reported mean change in IOP noted modest to no difference in IOP reduction. No trials reported on health-related quality of life, and the seven trials reported proportions of participants experiencing complications variably. Therefore, the association between treatment with iStent and quality of life or adverse events could not be estimated reliably from the data provided.

Overall completeness and applicability of evidence

Despite limiting this review to only RCTs, the included studies differed from one another in several regards. Recognizing these differences, we must consider several factors when interpreting the evidence.

1. Type and number of iStents may matter. Included studies suggested that implantation of two iStents, compared to one iStent, may be associated with greater proportions of participants who are drop-free and greater mean reduction in IOP in the long-term (Fernandez-Barrientos 2010; Katz 2015). However, a dearth of information precludes formal assessments of quality of life and adverse events associated with procedures involving implantation of multiple devices.
2. Specific racial or ethnic groups may be under-represented. Most participants randomized were white.
3. Prior treatments that participants received for glaucoma differed. All trials excluded people with laser glaucoma surgery performed within 30 days of screening and those with any prior incisional glaucoma surgery. Most trials required participants to be on one or more glaucoma medication at time of enrollment, except one trial that recruited treatment-naïve participants.
4. All seven trials received support from the Glaukos Corporation. Support included financial support to some/all authors, study devices, payment of article processing charges, and editorial assistance.

Quality of the evidence

The certainty of the evidence was low across comparisons included in this review. Most trials did not report how the random sequence was generated or the method of concealing allocation. There was high or unclear risk of detection bias in most trials because the outcome assessors were not masked. Attrition bias was either at high or unclear risk for four of the seven included trials. Additionally, few meta-analyses were possible due to considerable clinical, methodological, and statistical heterogeneity in interventions evaluated and length of participant follow-up. We also downgraded the evidence because only data from small studies sponsored by industry are available (Guyatt 2011). All seven studies were sponsored by the same industry sponsor (Table 3).

Potential biases in the review process

We worked with an information specialist to conduct a highly sensitive search of the literature and searched multiple databases including trial registries. Two review authors independently completed all steps outlined in the Methods section of this review to reduce bias during study selection, 'Risk of bias' assessment, and data extraction.

Agreements and disagreements with other studies or reviews

One Cochrane systematic review of combined surgery versus phacoemulsification alone for eyes with cataract and glaucoma examined interventions including the iStent (Zhang 2015). The authors included three trials of four that were also included in our review (Fea 2010; Fernandez-Barrientos 2010; Samuelson 2011). The authors reported a summary estimate for mean reduction in IOP at one year (MD −1.37 mmHg, 95% CI −2.76 to 0.03; I^2 = 56%), which we did not report due to substantial statistical heterogeneity and qualitative differences in effect estimates. Additionally, the authors extracted values for mean change from the medicated screening IOP rather than change from unmedicated (postwashout) IOP at baseline for one trial (Samuelson 2011).

We also identified two additional systematic reviews involving the iStent (Lavia 2017; Malvankar-Mehta 2015). Both reviews used inappropriate statistical methods in analyzing their data.

AUTHORS' CONCLUSIONS

Implications for practice

We identified very low-quality evidence comparing treatment of glaucoma using the iStent in combination with phacoemulsification to phacoemulsification alone. In the included trials, there was no difference in terms of keeping participants drop-free or in terms of mean reduction in intraocular pressure (IOP) from baseline. However, participants who received treatment with iStent in combination with phacoemulsification may have benefited from a modest reduction in number of IOP-lowering drops used per day, at a time point between six to 18 months, compared to those who underwent phacoemulsification alone. We have previously reported that people with glaucoma identify medication burden as an important outcome of their treatment, but rank other outcomes – such as IOP control and daily functioning – as more important (Le 2018b).

Due to substantial heterogeneity, we did not conduct a meta-analysis of the two studies comparing treatment with iStent to medical therapy. Investigators of those two studies did report, as expected, that no participants who were randomized to medical therapy were drop-free at 12 months, compared to over 90% in the iStent treatment groups. Additionally, data from one study suggested that treatment of participants with two or with three iStents may be more effective than treatment with one iStent. None of the seven included studies provided information on quality of life, and differences in adverse events between treatment groups were uncertain, given few reported events and wide confidence intervals of estimates. Evidence from 13 ongoing studies awaiting publication, once available, may clarify the harms and benefits of treating people with iStent devices. At present, clinical practice decisions should be based on provider judgment and patient preferences, given inconsistency in results and risk of bias in relevant studies published to date.

Implications for research

Given the large and increasing burden of glaucoma and growing interest in minimally invasive glaucoma surgical procedures involving devices such as the iStent, future research should evaluate the effects of these interventions on outcomes that are meaningful both clinically and to patients and regulators (Le 2016). IOP control – both percent lowering and absolute lowering – and medication burden are clinically meaningful outcomes and have been reported in all but two of the included trials: Fernandez-Barrientos 2010 reported mean IOP but not IOP lowering and NCT00721968 reported absolute IOP change but not percentage change. Safety outcomes are important to all stakeholders, but were only explicitly reported in two of the included trials (Samuelson 2011; Vold 2016).

Our findings show that no trials reported how the iStent affects quality of life. RCTs measuring outcomes that are important to patients can better inform regulatory decision-making, reimbursements, and other policy changes (Le 2016; Le 2018a). As a first step, research exploring patients' preferences in glaucoma therapy could identify or clarify outcomes that are important to those facing treatment decisions in the glaucoma clinic (Le 2018b; Tarver 2017). For example, in one survey of 274 patients seeking care in an academic glaucoma clinic, we observed that participants identified reduction in number of IOP-lowering medications as less important to them than maintaining the ability to perform vision-dependent activities, such as driving during the day or walking outside (Le 2018b). Functional outcome domains such as driving and mobility can be measured as patient-reported outcomes. In situations where data for clinical effectiveness may be unclear for a treatment, patient-reported outcomes and outcomes that reflect patients' preferences directly may provide a way to demonstrate the utility that treatment

ACKNOWLEDGEMENTS

We thank Kay Dickersin, Henry Jampel, Gus Gazzard, Barbara Hawkins, Kuang Hu, Riaz Qureshi, Anupa Shah, and Richard Wormald for their comments and suggestions during title registration and preparation of this review. This protocol was adapted from a Cochrane Review assessing the evidence for another minimally invasive glaucoma surgical (MIGS) procedure (Hu 2016). Cochrane Eyes and Vision (CEV) created and executed the electronic search strategies. We thank Anupa Shah for assisting with the review process. We thank Nitin Anand for peer reviewing the protocol and Jennifer Evans for her comments on the protocol. We are grateful to the following peer reviewers for their time and comments on the review: Henry Jampel, Ian Pitha, and Mark Lesselroth.

We thank the members of the MIGS Consortium for their input in this review.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Fea 2010

Methods	**Study design:** parallel-group RCT **Unit of randomization:** participant (1 eye per participant) **Number randomized:** 36 participants; 12 eyes of 12 participants in the 1 iStent in combination with phacoemulsification group and 24 eyes of 24 participants in phacoemulsification alone group **Unit of analysis:** participant (1 eye per participant) **Number analyzed:** 33 total; 12 eyes of 12 participants in the 1 iStent in combination with phacoemulsification group and 21 eyes of 21 participants in phacoemulsification alone group **Exclusions and losses to follow-up:** 3 participants in the phacoemulsification alone group (1 capsule rupture, 1 did not present at 6 months' follow-up, 1 died from complications from ankle surgery) **Handling of missing data:** analysis excluded participants lost to follow-up
Participants	**Country:** Torino, Italy (single site) **Age (mean ± SD):** 64.5 ± 3.4 years (range: 60–70 years) in the 1 iStent in combination with phacoemulsification group; 64.9 ± 3.1 years (range: 59–71 years) in the phacoemulsification alone group **Gender:** 4 men and 8 women in the 1 iStent in combination with phacoemulsification group; 9 men and 15 women in the phacoemulsification alone group **Medicated IOP (mean ± SD):** 17.9 ± 2.6 mmHg in the 1 iStent in combination with phacoemulsification group; 17.3 ± 3.0 mmHg in the phacoemulsification alone group **Inclusion criteria:** 1. previous diagnosis of POAG, scheduled for cataract surgery 2. IOP > 18 mmHg at 3 separate visits on ≥ 1 ocular hypotensive medications, or on ≥ 2 medications with uncontrolled IOP on 3 separate visits 3. preoperative corrected distance visual acuity ≤ 0.6 (20/80) 4. likely to follow surgeon instructions 5. able to give informed consent **Exclusion criteria:** 1. glaucoma diagnosis other than POAG (i.e. Scheie grade < 2) 2. presence of peripheral anterior synechiae 3. cloudy cornea likely to inhibit gonioscopic view of the angle 4. previous ocular surgery (including glaucoma-filtering surgery) 5. history of trauma or ocular surface disease 6. history of preproliferative or proliferative diabetic retinopathy 7. age-related macular degeneration with macular scar or large macular atrophy that would inhibit potential visual acuity

Fea 2010 *(Continued)*

	Diagnoses in participants: POAG and cataract
Interventions	**Intervention 1:** 1 iStent in combination with phacoemulsification **Intervention 2:** phacoemulsification alone **Length of follow-up:** 4 years
Outcomes	**Primary outcome:** mean IOP at 1, 2, 3, 6, 9, 12, 15, and 48 months **Secondary outcomes:** number and type of glaucoma medication; proportion of participants who "do not require ocular hypotensive medication"; mean change in IOP from baseline; mean IOP "after washout of ocular hypotensive agents"; and need for secondary intervention to control IOP at 1, 2, 3, 6, 9, 12, 15, and 48 months
Notes	**Type of study:** published **Enrollment start year:** 2006 **Funding source:** study devices provided by Glaukos Corporation, Laguna Hills, CA, USA; supported by Ricerca Finalizzata Della Regione Piemonte 2007 **Disclosures of interest:** "The author has no financial or proprietary interest in any material or method mentioned." **Publication language:** English **Trial registration:** NCT0084718

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Investigators used a computer random number generator. Quote: "Patient randomization was generated with a 2:1 ratio using Stata data analysis and statistical software."
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported.
Blinding of outcome assessment (detection bias) Number of IOP-lowering drops	Unclear risk	Unclear who assessed number of IOP-lowering drops.
Blinding of outcome assessment (detection bias) IOP measurement	Low risk	Investigators noted that "[p]atients were masked to their assignment, as were staff members who measured IOP throughout the study."
Incomplete outcome data (attrition bias) All outcomes	High risk	3/36 participants (all randomized to the phacoemulsification alone group) were excluded from the final analysis.
Selective reporting (reporting bias)	Low risk	Outcomes described in the results matched those specified in methods and in the ClinicalTrials.gov record.

Fea 2014

Methods	**Study design:** parallel-group RCT **Unit of randomization:** participant (1 eye per participant) **Number randomized:** 192 participants; 94 eyes of 94 participants in the iStent inject without combined phacoemulsification group and 98 eyes of 98 participants in the medical therapy group **Unit of analysis:** participant (1 eye per participant) **Number analyzed:** 192 participants; 94 eyes of 94 participants in the iStent inject without combined phacoemulsification and 98 eyes of 98 participants in the medical therapy group **Exclusions and losses to follow-up:** unclear **Handling of missing data:** not reported
Participants	**Country:** Italy, Spain, Poland, Germany, the UK, and Armenia (multi-centered) **Age (mean ± SD):** 64.5 ± 10.3 years in the iStent inject without combined phacoemulsification group; 64.3 ± 9.8 years in the medical therapy group **Gender:** 37 men and 57 women in the iStent inject without combined phacoemulsification group; 48 men and 50 women in the medical therapy **Medicated IOP (mean ± SD):** 21.1 ± 1.7 mmHg in the iStent inject without combined phacoemulsification group; 20.7 ± 1.7 mmHg in the medical therapy group **Inclusion criteria:** 1. previous diagnosis of POAG 2. age ≥ 18 years 3. mean IOP ≥ 22 mmHg and < 38 mmHg (unmedicated) 4. likely to be available 5. able to give informed consent **Exclusion criteria:** 1. known non-responders to latanoprost 2. secondary glaucoma 3. prior incisional glaucoma surgery 4. cloudy cornea 5. signs of traumatic or uveitic, neovascular, or angle-closure glaucoma **Diagnoses in participants:** POAG, PEXG, or PG
Interventions	**Intervention 1:** iStent inject without combined phacoemulsification **Intervention 2:** medical therapy, consisting of a fixed combination of latanoprost/timolol (Xalacom; Pfizer, New York, NY, USA) **Length of follow-up:** 4 years
Outcomes	**Primary outcome:** mean IOP at 12 months **Secondary outcomes:** proportion of participants who achieved an IOP reduction ≥ 20% vs baseline unmedicated IOP; proportion of participants who achieved an IOP reduction ≤ 18 mmHg; mean change in IOP from baseline; proportion of participants who achieved an IOP reduction ≥ 30% vs baseline unmedicated IOP; proportion of participants who achieved an IOP reduction ≥ 40% vs baseline unmedicated IOP; proportion of participants who achieved an IOP reduction ≥ 50% vs baseline unmedicated IOP; and proportion of participants taking medication at 12 months

Fea 2014 *(Continued)*

	Safety outcomes: vertical C:D ratio; eye burning; medication allergy; soreness/discomfort
Notes	**Type of study:** published **Enrollment start year:** 2009 **Funding source:** Glaukos Corporation, Laguna Hills, CA, USA provided study devices, sponsorship for performing this study, editorial assistance, and payment of article processing charges. **Disclosures of interest:** "The authors report no conflicts of interest in this work." **Publication language:** English **Trial registration:** NCT00913029

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random sequence generation method not reported.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported.
Blinding of outcome assessment (detection bias) Number of IOP-lowering drops	High risk	Investigators describe a limitation of the study as "not a masked study due to the disparate forms of therapy."
Blinding of outcome assessment (detection bias) IOP measurement	High risk	Investigators describe a limitation of the study as "not a masked study due to the disparate forms of therapy."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Completeness of outcome data varied between time points; some participants omitted from analysis at 1 time point returned at the next.
Selective reporting (reporting bias)	Low risk	Outcomes described in the results matched those specified in methods and in the ClinicalTrials.gov record.

Fernandez-Barrientos 2010

Methods	**Study design:** parallel-group RCT **Unit of randomization:** participant (1 eye per participant) **Number randomized:** 33 participants; 17 eyes of 17 participants in the 2 iStents in combination with phacoemulsification group and 16 eyes of 16 participants in the phacoemulsification alone group **Unit of analysis:** participants (1 eye per participant) **Number analyzed:** 33 participants; 17 eyes of 17 participants in the 2 iStents in combination with phacoemulsification group and 16 eyes of 16 participants in the phacoemulsification alone group **Exclusions and losses to follow-up:** 0 for IOP study; intention-to-treat analysis
Participants	**Country:** Madrid, Spain (3 sites)

Fernandez-Barrientos 2010 *(Continued)*

Age (mean ± SD): 75.2 ± 7.2 years (range: 63–86 years) in the 2 iStents in combination with phacoemulsification group; 76.7 ± 5.8 years (range: 64–89 years) in phacoemulsification alone group

Gender: 6 men and 11 women in the 2 iStents in combination with phacoemulsification group; 9 men and 7 women in the phacoemulsification alone group

Medicated IOP: not reported

Inclusion criteria:

1. age ≥ 18 years
2. cataract requiring surgery
3. IOP > 17 mmHg and < 31 mmHg with treatment and > 21 mmHg and < 36 mmHg after the pharmacologic washout period
4. minimum visual acuity 20/200 or better; worse than 20/40
5. authorization and signature of informed consent

Exclusion criteria:

1. age < 18 years
2. closed-angle glaucoma
3. secondary glaucoma; non-neovascular, uveitic, or angular recession glaucoma
4. previous glaucoma procedures (e.g. trabeculectomy, viscocanalostomy, argon laser trabeculoplasty, selective laser trabeculoplasty, drainage implant, collagen implant, cyclodestruction procedure)
5. glaucoma due to burns with chemical elements
6. peripheral anterior synechiae in the area where the implant was to be inserted
7. cornea with opacity that impedes gonioscopy vision from the nasal angle, or scleral spur not clearly visible, or both
8. glaucoma due to vascular disorder
9. previous refractive surgery that makes IOP measures difficult
10. ocular surface disorders
11. chronic inflammatory disease
12. previous ocular trauma
13. retrobulbar tumor
14. Sturge Weber syndrome
15. thyroid ocular illness
16. elevated episcleral venous pressure due to a history of thyroid orbitopathy, carotid cavernous fistula, orbital tumor, or congestive orbital illness
17. threat of visual field fixation

Diagnoses in participants: OHT or OAG in need of cataract surgery

Interventions	**Intervention 1:** 2 iStents in combination with phacoemulsification **Intervention 2:** phacoemulsification alone **Study follow-up:** 12 months
Outcomes	Mean outflow facility rate; anterior chamber volume; anterior chamber distance; anterior chamber angle; aqueous flow; mean IOP; number of ocular hypotensive medication; BCVA; gonioscopic findings; slit lamp biomicroscopy findings; dilated funduscopic exam; and visual field measurements (Octobpus 301 G1 TOP) at 1, 6, and 12 months
Notes	**Type of study:** published **Enrollment start year:** 2006 **Funding source:** supported by Glaukos Corporation, Laguna Hills, CA, USA

Fernandez-Barrientos 2010 *(Continued)*

Disclosures of interest: authors disclosed having received financial support, consulting, being the recipient of gifts, or a combination of these from the Glaukos Corporation

Publication language: English

Trial registration: NCT00326066

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Investigators used a "computer-generated sequence" to assign eligible participants.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported.
Blinding of outcome assessment (detection bias) Number of IOP-lowering drops	Low risk	Investigators noted that all postoperative evaluations "were performed by the same examiner (YFB), who was masked to the type of surgery performed."
Blinding of outcome assessment (detection bias) IOP measurement	Low risk	Investigators noted that all postoperative evaluations "were performed by the same examiner (YFB), who was masked to the type of surgery performed."
Incomplete outcome data (attrition bias) All outcomes	Low risk	No incomplete outcome data for IOP; authors reported conducting an intention-to-treat analysis.
Selective reporting (reporting bias)	Low risk	Outcomes described in the results matched those specified in methods and in the ClinicalTrials.gov record.

Katz 2015

Methods	**Study design:** parallel-group RCT **Unit of randomization:** participant (1 eye per participant) **Number randomized:** 119 participants; 38 eyes of 38 participants in the 1 iStent without phacoemulsification group, 41 eyes of 41 participants in the 2 iStents without phacoemulsification group, and 40 eyes of 40 participants in the 3 iStents without phacoemulsification group **Unit of analysis:** participants (1 eye per participant) **Number analyzed:** 119 participants; 38 eyes of 38 participants in the 1 iStent without phacoemulsification group, 41 eyes of 41 participants in the 2 iStents without phacoemulsification group, and 40 eyes of 40 participants in the 3 iStents without phacoemulsification group **Exclusions and losses to follow-up:** complete records through 18 months were available for 119 participants
Participants	**Country:** Yerevan, Armenia (single-site) **Age (mean ± SD):** 68.1 ± 9.1 years (range: 49–83 years) in the 1 iStent without phacoemulsification group, 67.8 ± 9.3 years (range: 51–83 years) in the 2 iStents without phacoemulsification group, and 60.9 ± 8.1 years (range: 49–85 years) in the 3 iStents without phacoemulsification group

Katz 2015 *(Continued)*

Gender: 23 men and 15 women in the 1 iStent without phacoemulsification group, 21 men and 20 women in the 2 iStents without phacoemulsification group, and 17 men and 23 women in the 3 iStents without phacoemulsification group

Medicated IOP (mean ± SD): 19.8 ± 1.3 mmHg in the 1 iStent without phacoemulsification group, 20.1 ± 1.6 mmHg in the 2 iStents without phacoemulsification group, and 20.4 ± 1.8 mmHg in the 3 iStents without phacoemulsification group

Inclusion criteria:

1. mild-to-moderate OAG not controlled on 2 preoperative medications
2. IOP ≥ 18 mmHg and ≤ 30 mmHg (medicated); > 22 mmHg and < 38 mmHg (unmedicated)
3. C:D ratio ≤ 0.9
4. normal angle anatomy
5. absence of peripheral anterior synechia, rubeosis, or other angle abnormalities

Exclusion criteria:

1. pseudophakia with anterior-chamber intraocular lens
2. prior stent implantation in the study eye
3. traumatic, uveitic, neovascular, or angle-closure glaucoma
4. glaucoma associated with vascular disorders
5. functionally significant visual field loss
6. prior incisional glaucoma surgery
7. prior selective laser trabeculoplasty within 90 days of screening
8. prior argon laser trabeculoplasty
9. iridectomy or laser iridotomy
10. visual field status at risk
11. active corneal inflammation or edema
12. clinically significant corneal dystrophy
13. corneal surgery of any type
14. corneal opacities
15. congenital or traumatic cataract
16. retinal or optic nerve disorders
17. elevated episcleral venous pressure
18. clinically significant sequelae from trauma
19. chronic ocular inflammatory disease
20. BCVA worse than 20/200
21. fellow eye in the trial
22. pregnant or nursing women

Diagnoses in participants: POAG, PEXG, or PG; and phakic

Interventions	**Intervention 1:** 1 iStent without phacoemulsification **Intervention 2:** 2 iStents without phacoemulsification **Intervention 3:** 3 iStents without phacoemulsification **Study follow-up:** 5 years
Outcomes	**Primary outcome**: "month 12 IOP reduction from baseline unmedicated IOP of ≤20%, without use of topical ocular medications at 12 months and without secondary glaucoma surgical procedures by the 12-month visit." **Secondary outcomes:** "month 12 IOP ≤18 mmHg IOP, without use of topical ocular medications at 12 months and without secondary glaucoma surgical procedures by the 12-month visit. Additional efficacy measures included proportional analyses of month 12 IOP ≤15 mmHg, without use of topical ocular

Katz 2015 *(Continued)*

	medications at 12 months and without secondary glaucoma surgical procedures by the 12-month visit, mean IOP and medication usage through 18 months postoperatively, and month 18 unmedicated mean IOP and change in IOP from preoperative values." **Safety outcomes:** "assessment of BCVA, visual field via perimetry, slit-lamp evaluation, C:D ratio estimation, corneal thickness via pachymetry, complications, and ocular adverse events"
Notes	**Type of study:** published (longest follow-up reported: 42 months) **Enrollment start year:** 2012 **Funding source:** Glaukos Corporation, Laguna Hills, CA, USA provided study devices, sponsorship for performing this study, data collection, data management, data analysis, and editorial assistance. **Disclosures of interest:** authors disclosed having received financial support, consulting, being the recipient of gifts, or a combination of these from the Glaukos Corporation **Publication language:** English **Trial registration:** NCT01517477

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random sequence generation method not reported.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported.
Blinding of outcome assessment (detection bias) Number of IOP-lowering drops	High risk	Investigators describe the trial as an "open-label study design, a single-site study [which] lack[s] of masking to the study-treatment groups."
Blinding of outcome assessment (detection bias) IOP measurement	High risk	Investigators describe the trial as an "open-label study design, a single-site study [which] lack[s] of masking to the study-treatment groups."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete records through 18 months were available for 119 participants.
Selective reporting (reporting bias)	Low risk	Outcomes described in the results matched those specified in methods and in the ClinicalTrials.gov record.

NCT00721968

Methods	**Study design:** parallel-group RCT **Unit of randomization:** participant (1 eye per participant) **Number randomized:** 44 participants; 27 eyes of 27 participants in the 1 iStent in combination with phacoemulsification group and 17 eyes of 17 participants in phacoemulsification alone group **Unit of analysis:** participant (1 eye per participant)

NCT00721968 *(Continued)*	**Number analyzed:** 44 participants; 27 eyes of 27 participants in the 1 iStent in combination with phacoemulsification group and 17 eyes of 17 participants in phacoemulsification alone group **Exclusions and losses to follow-up:** 2 participants in the 1 iStent in combination with phacoemulsification group lost to follow-up **Handling of missing data:** not reported
Participants	**Country:** US (multiple sites) **Age:** not reported **Gender:** 7 men and 20 women in the 1 iStent in combination with phacoemulsification group; 7 men and 10 women in the phacoemulsification alone group **Medicated IOP:** not reported **Inclusion criteria:** 1. mild-to-moderate OAG in need of cataract surgery 2. willing to attend scheduled follow-up exams for 2 years postoperatively 3. willing to provide informed consent **Exclusion criteria:** 1. not meeting inclusion criteria **Diagnoses in participants:** OAG in need of cataract surgery
Interventions	**Intervention 1:** 1 iStent in combination with phacoemulsification **Intervention 2:** phacoemulsification alone **Length of follow-up:** 1 year
Outcomes	**Primary outcome:** proportion of participants with IOP ≤ 18 mmHg without topical hypotensive medications at 12 months **Other outcome:** number of ocular hypotensive medications by visit and at 12 months
Notes	**Type of study:** study results available on ClinicalTrials.gov **Enrollment start year:** 2007 **Funding source:** supported by Glaukos Corporation, Laguna Hills, CA, USA **Disclosures of interest:** not reported **Publication language:** English **Trial registration:** NCT00721968

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random sequence generation method not reported.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported.

NCT00721968 *(Continued)*

Blinding of outcome assessment (detection bias) Number of IOP-lowering drops	High risk	Masking described as "None (Open Label)."
Blinding of outcome assessment (detection bias) IOP measurement	High risk	Masking described as "None (Open Label)."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Study results available only on ClinicalTrials.gov.
Selective reporting (reporting bias)	Unclear risk	Study results available only on ClinicalTrials.gov.

Samuelson 2011

Methods	**Study design:** parallel-group RCT **Unit of randomization:** participants (1 eye per participant) **Number randomized:** 240 participants; 117 eyes of 116 participants in the 1 iStent in combination with phacoemulsification group and 123 eyes of 123 participants in phacoemulsification alone group **Unit of analysis:** participants (1 eye per participant) **Number analyzed:** 240 participants (intention-to-treat); 117 eyes of 116 participants in the 1 iStent in combination with phacoemulsification group and 123 eyes of 123 participants in phacoemulsification alone group **Exclusions and losses to follow-up:** 22 eyes/participants; 15 eyes of 15 participants were excluded (6 in the 1 iStent in combination with phacoemulsification group and 9 in the phacoemulsification group) at 12 months, and 7 eyes of 7 participants were lost to follow-up (5 in the 1 iStent in combination with phacoemulsification group and 2 in phacoemulsification alone group) at 12 months **Handling of missing data:** intention-to-treat; last observation carried forward analysis
Participants	**Country:** US (29 sites) **Age (mean ± SD):** 74.0 ± 8.0 years (range: 53–88 years) in combined surgery group; 73.0 ± 9.0 years (range: 48–88 years) in cataract surgery alone group **Gender:** 46 men and 71 women in the 1 iStent in combination with phacoemulsification group; 52 men and 71 women in the phacoemulsification group **Medicated IOP (mean ± SD):** 18.7 ± 3.3 mmHg in the 1 iStent in combination with phacoemulsification group; 18.0 ± 3.0 mmHg in the phacoemulsification alone group **Inclusion criteria:** 1. mild-to-moderate OAG confirmed by gonioscopy, with definitive characteristic visual field or nerve pathology 2. IOP ≤ 24 mmHg while taking 1–3 ocular hypotensive medications, with a stable medication regimen for ≥ 2 months 3. after a washout of ocular hypotensive medication, IOP ≥ 22 mmHg and ≤ 36 mmHg "during normal office hours" 4. presented with the need for cataract surgery, defined as clinically significant cataract with BCVA of 20/40 or worse in the presence of glare

Samuelson 2011 *(Continued)*

	5. C:D ratio ≤ 0.8 **Exclusion criteria:** 1. severe glaucomatous field defects 2. severely uncontrolled IOP 3. angle-closure glaucoma 4. neovascular, uveitic, or angle recession glaucoma 5. previous glaucoma surgery other than iridectomy 6. previous refractive procedures 7. known corticosteroid responders 8. ocular disease that would affect safety 9. people with monocular vision 10. fellow eye BCVA worse than 20/200 **Diagnoses in participants:** OAG, PEXG, and PG; and in need of cataract surgery
Interventions	**Intervention 1:** 1 iStent in combination with phacoemulsification **Intervention 2:** phacoemulsification alone **Length of follow-up:** 2 years
Outcomes	**Primary outcome:** proportion of participants with IOP ≤ 21 mmHg without ocular hypotensive medication at 12 and 24 months **Secondary outcomes:** proportion of participants with ≥ 20% reduction in IOP from baseline without medication; mean reduction in IOP; mean number of ocular hypotensive medications at 12 months; mean decrease in medications from screening; and mean IOP at 12 and 24 months **Safety outcomes:** loss of BCVA of ≥ 1 line ≥ 3 months postoperative; secondary surgical intervention; infection; elevated IOP requiring treatment with oral or intravenous medication or surgical intervention; stent obstruction; corneal thickness; cataract surgery; mean deviation in visual field; frequently reported postoperative ocular complications (≥ 3%); and other complications at 12 and 24 months
Notes	**Type of study:** published **Enrollment start year:** 2005 **Funding source:** Glaukos Corporation, Laguna Hills, CA, USA provided funding/support **Disclosures of interest:** investigators reported receiving financial support from or consulting for Alcon, Allergan, AMO, AqueSys, Glaukos, iScience, Ivantis, Lumenis, Pfizer, QLT, and Santen; all trial investigators were consultants to Glaukos for the conduct of this study; 4 trial investigators are equity owners of Glaukos **Publication language:** English **Trial registration:** NCT00323284

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Investigators noted that a "[c]omputer-generated randomization was performed (PROC PLAN, PC-SAS, SAS Inc., Cary NC)."
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported.

Samuelson 2011 *(Continued)*

Blinding of outcome assessment (detection bias) Number of IOP-lowering drops	High risk	Quote: "The study was, by design, open-label, given that there was no way to mask the treatment to the surgeon during the surgical intervention, or to the observer at the time of gonioscopy."
Blinding of outcome assessment (detection bias) IOP measurement	High risk	Quote: "The study was, by design, open-label, given that there was no way to mask the treatment to the surgeon during the surgical intervention, or to the observer at the time of gonioscopy."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Investigators excluded 22/240 (9%) participants from the 12-month analysis, among whom 11/117 were in the 1 iStent in combination with phacoemulsification and 11/123 were in cataract surgery alone group.
Selective reporting (reporting bias)	Low risk	Outcomes described in the results matched those specified in methods and in the ClinicalTrials.gov record.

Vold 2016

Methods	**Study design:** parallel-group RCT **Unit of randomization:** participant (1 eye per participant) **Number randomized:** 101 participants; 54 eyes of 54 participants in the 2 iStents without combined phacoemulsification and 47 eyes of 47 participants in medical therapy group **Unit of analysis:** participant (1 eye per participant) **Number analyzed:** 73 participants; 39 eyes of 94 participants in the 2 iStents without combined phacoemulsification and 34 eyes of 34 participants in medical therapy group **Exclusions and losses to follow-up:** unclear; data not available for 28 participants at 36 months **Handling of missing data:** available case
Participants	**Country:** Yerevan, Armenia (single site) **Age (mean ± SD):** 64.5 ± 11.1 years in the 2 iStents without combined phacoemulsification group; 62.0 ± 11.1 years in the medical therapy group **Gender:** 37 men and 57 women in the 2 iStents without combined phacoemulsification group; 48 men and 50 women in the medical therapy **Medicated IOP (mean ± SD):** not applicable; enrolled only treatment-naïve participants **Inclusion criteria:** 1. people with phakia with newly diagnosed primary OAG, PEX, or OHT 2. have not undergone prior treatment of any type 3. IOP ≥ 21 mmHg and ≤ 40 mmHg 4. C:D ratio ≤ 0.9 5. normal angle anatomy **Exclusion criteria:** 1. uveitic, neovascular, or angle-closure glaucoma 2. glaucoma associated with vascular disorders 3. corneal pathology or prior corneal surgery 4. congenital or traumatic cataract or prior cataract surgery

Vold 2016 *(Continued)*

	5. retinal or optic nerve disorders 6. any ocular disease or condition that "in the opinion of the investigator, would place the subject at significant risk, confound study results, or interfere with study participation" 7. fellow eye in clinical trials 8. pregnant or nursing women **Diagnoses in participants:** POAG, PEXG, or PG
Interventions	**Intervention 1:** 2 iStents without combined phacoemulsification **Intervention 2:** medical therapy, consisting of topical travoprost (Travatan 0.004%; Alcon, Fort Worth, TX, USA) **Length of follow-up:** 3 years
Outcomes	**Primary outcomes:** mean IOP regardless of additional medical therapy; mean IOP in eyes that had not received additional therapy after initial treatment at 12, 24, and 36 months **Secondary outcomes:** proportion of eyes with postoperative IOP ≤ 18 mmHg without additional medical therapy; proportion of eyes with postoperative IOP ≤ 15 mmHg without additional medical therapy; number of participants for whom medication had been added; at 12, 24, and 36 months **Safety outcomes:** adverse events and complications; mean deviation in visual field; mean C:D ratio; mean central corneal thickness; proportion of participants with BCVA 20/40 or better, 20/100, and 20/100 separately; at 12, 24, and 36 months; proportion of participants with progression of cataract and proportion of participants with need for cataract surgery at 36 months
Notes	**Type of study:** published **Funding source:** Glaukos Corporation, Laguna Hills, CA, USA provided funding/support **Disclosures of interest:** investigators reported receiving non-financial, financial, and non-study financial support from Glaukos **Publication language:** English **Trial registration:** NCT01443988

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random sequence generation method not reported.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported.
Blinding of outcome assessment (detection bias) Number of IOP-lowering drops	High risk	Investigators described the study as employing an "open-label unmasked strategy" and "neither subjects nor clinicians were masked to treatment."
Blinding of outcome assessment (detection bias) IOP measurement	High risk	Investigators described the study as employing an "open-label unmasked strategy" and "neither subjects nor clinicians were masked to treatment."
Incomplete outcome data (attrition bias) All outcomes	High risk	Available case analysis of 73/101 (72%) participants at 36 months.

Vold 2016 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Some differences between trial registration and trial report: outcomes modified screening in mean diurnal IOP (mmHg) at the month 12 visit to mean IOP reduction at 3 years; diurnal measurements of IOP were not performed.

BCVA: best-corrected visual acuity; C:D: cup-to-disk; IOP: intraocular pressure; OAG: open-angle glaucoma; OHT: ocular hypertension; PEXG: pseudoexfoliative glaucoma; PG: pigmentary glaucoma; POAG: primary open-angle glaucoma; RCT: randomized controlled trial; SD: standard deviation.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Bacharach 2014	Not a randomized controlled trial
NCT03274323	Study was withdrawn before enrolling participants
Vlasov 2017	Not a randomized controlled trial

Characteristics of ongoing studies *[ordered by study ID]*

EUCTR2009-018066-36-ES

Trial name or title	Evaluación aleatorizada prospectiva en abierto del iStent® (GTS400) frente a dos agentes hipotensores oculares en pacientes con glaucoma primario de ángulo abierto – second line study [Open prospective randomized evaluation of iStent® (GTS400) versus two ocular hypotensive agents in patients with primary open-angle glaucoma]
Methods	**Study design:** parallel-group RCT **Unit of randomization:** not reported **Number randomized:** not reported **Unit of analysis:** not reported **Number analyzed:** not reported **Exclusions and losses to follow-up:** not reported **Handling of missing data:** not reported
Participants	**Country:** Spain **Age:** not reported **Gender:** not reported **Inclusion criteria:** 1. Diagnosis by researchers of primary open angle glaucoma (including pseudoexfoliation or pigmentary glaucoma) 2. Male or female, at least 18 years of age and able to give written informed consent 3. Diurnal untreated mean IOP (at the initial visit after having rested from all medication taken) of at least 22 mmHg, but less than 38 mmHg 4. The scleral spur of the patient must be clearly visible with the gonioscope 5. Able to attend follow-up visits

EUCTR2009-018066-36-ES *(Continued)*

	6. No prior incisional surgery or laser interventions to treat glaucoma; previous surgery for cataracts is acceptable 7. Minimum BCVA of 20/200 or better **Exclusion criteria:** not reported (in Spanish) **Diagnoses in participants:** OAG
Interventions	**Intervention 1:** iStent **Intervention 2:** latanoprost; timolol **Length of follow-up:** not reported
Outcomes	**Primary outcomes:** Mean IOP at each visit for the study; mean reduction in IOP; percentage of patients achieving an objective IOP> 18 mmHG; responses to the patient's questionnaire **Secondary outcomes:** not reported **Safety outcomes:** not reported
Starting date	11 March 2010
Contact information	No contact details
Notes	**Type of study:** awaiting classification **Funding source:** Glaukos Corporation, Laguna Hills, CA, USA provided funding/support **Disclosures of interest:** not reported **Publication language:** not reported **Trial registration:** EudraCT Number 2009-018066-36

NCT00326079

Trial name or title	A study of the Glaukos trabecular micro-bypass stent in open angle glaucoma subjects 1 stent versus 2
Methods	**Study design:** parallel-group RCT **Unit of randomization:** not reported **Number randomized:** not reported **Unit of analysis:** not reported **Number analyzed:** not reported **Exclusions and losses to follow-up:** not reported **Handling of missing data:** not reported
Participants	**Country:** Austria, Germany, Spain, Turkey **Age:** not reported **Gender:** not reported **Inclusion criteria:**

NCT00326079 *(Continued)*

	1. diagnosed with OAG 2. taking ≥ 1 glaucoma medication 3. signed informed consent **Exclusion criteria:** 1. angle closure glaucoma 2. secondary glaucomas except pseudoexfoliative and pigmentary; no neovascular, uveitic, or angle recession glaucoma 3. prior glaucoma procedures (e.g. trabeculectomy, viscocanalostomy, ALT, SLT, shunt implant, collagen implant, cyclodestructive procedures, etc.) 4. fellow eye already enrolled **Diagnoses in participants:** OAG
Interventions	**Intervention 1:** implantation of 1 Glaukos iStent **Intervention 2:** implantation of 2 Glaukos iStents **Length of follow-up:** 2 years
Outcomes	**Primary outcomes:** efficacy at 2 years **Secondary outcomes:** IOP measurement from preoperative baseline; incidence of adverse events during the surgical procedure and postoperative period **Safety outcomes:** (see secondary outcomes)
Starting date	August 2004
Contact information	No contact details
Notes	**Type of study:** awaiting classification – described as unknown on ClinicalTrials.gov **Funding source:** Glaukos Corporation, Laguna Hills, CA, USA provided funding/support **Disclosures of interest:** not reported **Publication language:** not reported **Trial registration:** NCT00326079

NCT01052558

Trial name or title	GTS400 stent implantation in conjunction with cataract surgery in subjects with open-angle glaucoma
Methods	**Study design:** parallel-group RCT **Unit of randomization:** not reported **Number randomized:** not reported **Unit of analysis:** not reported **Number analyzed:** not reported **Exclusions and losses to follow-up:** not reported **Handling of missing data:** not reported

NCT01052558 *(Continued)*

Participants	**Country:** US **Age:** not reported **Gender:** not reported **Inclusion criteria:** 1. diagnosed with OAG in the study eye 2. using 1–3 glaucoma medications 3. able and willing to attend follow-up visits for 2 years postoperation 4. able and willing to sign informed consent **Exclusion criteria:** 1. PEXG and PG 2. prior glaucoma surgery of any type **Diagnoses in participants:** OAG
Interventions	**Intervention 1:** cataract surgery with subsequent implantation of GTS400 stents **Intervention 2:** cataract surgery **Length of follow-up:** 1 year
Outcomes	**Primary outcomes:** proportion of participants with 12-month diurnal IOP ≤ 21 mmHg without use of ocular hypotensive medications for ≥ 4 weeks prior to 12-month visit **Secondary outcomes:** not reported **Safety outcomes:** not reported
Starting date	20 January 2010
Contact information	No contact details
Notes	**Type of study:** awaiting classification – described as "completed" on ClinicalTrials.gov **Funding source:** Glaukos Corporation, Laguna Hills, CA, USA provided funding/support **Disclosures of interest:** not reported **Publication language:** not reported **Trial registration:** NCT01052558

NCT01252849

Trial name or title	Purpose of this study is to evaluate the safety and efficacy of one, two, or three iStents for the reduction of intraocular pressure in open-angle glaucoma subjects
Methods	**Study design:** parallel-group RCT **Unit of randomization:** not reported **Number randomized:** not reported **Unit of analysis:** not reported

NCT01252849 *(Continued)*

	Number analyzed: not reported **Exclusions and losses to follow-up:** not reported **Handling of missing data:** not reported
Participants	**Country:** Armenia **Age:** not reported **Gender:** not reported **Inclusion criteria:** 1. diagnosed with POAG 2. using 2 topical hypotensive medications **Exclusion criteria:** 1. traumatic, uveitic, neovascular, or angle closure glaucoma 2. fellow eye already enrolled **Diagnoses in participants:** POAG
Interventions	**Intervention 1:** implantation of 1 iStent through a small temporal clear corneal incision **Intervention 2:** implantation of 2 iStents through a small temporal clear corneal incision **Intervention 3:** implantation of 3 iStents through a small temporal clear corneal incision **Length of follow-up:** 1 year
Outcomes	**Primary outcomes:** mean diurnal IOP reduction ≥ 20% at month 12 vs baseline at 1 year **Secondary outcomes:** mean diurnal IOP < 18 mmHg at 1 year **Safety outcomes:** not reported
Starting date	3 December 2010
Contact information	No contact details
Notes	**Type of study:** awaiting classification POAG described as "active, not recruiting" on ClinicalTrials.gov **Funding source:** Glaukos Corporation, Laguna Hills, CA, USA provided funding/support **Disclosures of interest:** not reported **Publication language:** not reported **Trial registration:** NCT01252849

NCT01444040

Trial name or title	Subjects with open-angle glaucoma, pseudoexfoliative glaucoma, or ocular hypertension naïve to medical and surgical therapy, treated with two trabecular micro-bypass stents (iStent inject) or travoprost
Methods	**Study design:** parallel-group RCT

NCT01444040 *(Continued)*

	Unit of randomization: not reported **Number randomized:** not reported **Unit of analysis:** not reported **Number analyzed:** not reported **Exclusions and losses to follow-up:** not reported **Handling of missing data:** not reported
Participants	**Country:** Armenia **Age:** not reported **Gender:** not reported **Inclusion criteria:** 1. phakic study eye 2. IOP ≥ 21 mmHg and ≤ 40 mmHg at the screening visit (people with OHT require a second screening IOP measurement **Exclusion criteria:** 1. aphakic or pseudophakic eyes (AC-IOLs or PC-IOLs) 2. previous usage of topical prostaglandin analogues or prior medical therapy for glaucoma **Diagnoses in participants:** OAG
Interventions	**Intervention 1:** implantation of 2 iStent inject devices **Intervention 2:** travoprost drops **Length of follow-up:** 5 years
Outcomes	**Primary outcomes:** change from screening in mean diurnal IOP (mmHg) at 1 year **Secondary outcomes:** change in mean diurnal IOP vs screening at 2 years; change in screening in time-wise IOPs at "Various Month 12-60"; proportion of responders at "Various 12-60 months." "A responder is defined as a subject with a certain target IOP value or a certain reduction of IOP as compared to screening." **Safety outcomes:** not reported
Starting date	30 September 2011
Contact information	No contact details
Notes	**Type of study:** awaiting classification PC-IOL described as "Active, not recruiting" on ClinicalTrials.gov **Funding source:** Glaukos Corporation, Laguna Hills, CA, USA provided funding/support **Disclosures of interest:** not reported **Publication language:** not reported **Trial registration:** NCT01444040

NCT01444105

Trial name or title	Open-angle glaucoma subjects on one ocular hypotensive medication randomized to treatment with two trabecular micro-bypass stents or selective laser trabeculoplasty
Methods	**Study design:** parallel-group RCT **Unit of randomization:** not reported **Number randomized:** not reported **Unit of analysis:** not reported **Number analyzed:** not reported **Exclusions and losses to follow-up:** not reported **Handling of missing data:** not reported
Participants	**Country:** Armenia **Age:** not reported **Gender:** not reported **Inclusion criteria:** 1. phakic study eye requiring cataract removal and PC-IOL implantation 2. POAG (including PG or PEXG) **Exclusion criteria:** 1. aphakic or pseudophakic with PC-IOL or AC-IOL (study eye) 2. prior stent implantations (study eye) **Diagnoses in participants:** OAG
Interventions	**Intervention 1:** implantation of 2 iStent devices **Intervention 2:** SLT laser treatment **Length of follow-up:** not reported
Outcomes	**Primary outcomes:** change from baseline in mean diurnal IOP (mmHg) at 1 year **Secondary outcomes:** not reported **Safety outcomes:** not reported
Starting date	30 September 2011
Contact information	No contact details
Notes	**Type of study:** awaiting classification, PC-IOL described as "active, not recruiting" on ClinicalTrials.gov **Funding source:** Glaukos Corporation, Laguna Hills, CA, USA provided funding/support **Disclosures of interest:** not reported **Publication language:** not reported **Trial registration:** NCT01444105

NCT01455467

Trial name or title	Open-angle glaucoma subjects on one topical hypotensive medication randomized to treatment with one or two trabecular micro-bypass stents in conjunction with cataract surgery
Methods	**Study design:** parallel-group RCT **Unit of randomization:** not reported **Number randomized:** not reported **Unit of analysis:** not reported **Number analyzed:** not reported **Exclusions and losses to follow-up:** not reported **Handling of missing data:** not reported
Participants	**Country:** Armenia **Age:** not reported **Gender:** not reported **Inclusion criteria:** 1. phakic study eye requiring cataract removal and PC-IOL implantation 2. POAG (including PG or PEXG) **Exclusion criteria:** 1. aphakic or pseudophakic with PC-IOLs or AC-IOLs (study eye) 2. prior stent implantations (study eye) **Diagnoses in participants:** OAG
Interventions	**Intervention 1:** implantation of 1 iStent in conjunction with cataract surgery **Intervention 2:** implantation of 2 iStent in conjunction with cataract surgery **Length of follow-up:** 1 year
Outcomes	**Primary outcomes:** mean diurnal IOP reduction of ≥ 20% vs baseline mean diurnal IOP at 1 year **Secondary outcomes:** not reported **Safety outcomes:** not reported
Starting date	20 October 2011
Contact information	No contact details
Notes	**Type of study:** awaiting classification, described as "active, not recruiting" on ClinicalTrials.gov **Funding source:** Glaukos Corporation, Laguna Hills, CA, USA provided funding/support **Disclosures of interest:** not reported **Publication language:** not reported **Trial registration:** NCT01455467

NCT01461291

Trial name or title	Multicenter study using Glaukos® trabecular micro-bypass stent model GTS400 using the G2-M-IS injector system in conjunction with cataract surgery
Methods	**Study design:** parallel-group RCT **Unit of randomization:** not reported **Number randomized:** not reported **Unit of analysis:** not reported **Number analyzed:** not reported **Exclusions and losses to follow-up:** not reported **Handling of missing data:** not reported
Participants	**Country:** US **Age:** not reported **Gender:** not reported **Inclusion criteria:** 1. mild-to-moderate OAG 2. characteristics consistent with mild/moderate glaucoma 3. use of 1–3 medications at time of screening exam **Exclusion criteria:** 1. PG or PEXG 2. prior incisional glaucoma surgery **Diagnoses in participants:** POAG
Interventions	**Intervention 1:** implantation of 2 GTS400 stents using G2-M-IS iStent inject **Intervention 2:** cataract surgery alone **Length of follow-up:** 2 years
Outcomes	**Primary outcomes**: ≥ 20% reduction in IOP at 2 years **Secondary outcomes:** diurnal IOP reduction from baseline at 2 years **Safety outcomes:** not reported
Starting date	28 October 2011
Contact information	No contact details
Notes	**Type of study:** awaiting classification, described as "active, not recruiting" on ClinicalTrials.gov **Funding source:** Glaukos Corporation, Laguna Hills, CA, USA provided funding/support **Disclosures of interest:** not reported **Publication language:** not reported **Trial registration:** NCT01461291

NCT02023242

Trial name or title	Comparing effectiveness of the Hydrus Microstent (TM) to two iStents to lower IOP in phakic eyes (COMPARE)
Methods	**Study design:** parallel-group RCT **Unit of randomization:** not reported **Number randomized:** not reported **Unit of analysis:** not reported **Number analyzed:** not reported **Exclusions and losses to follow-up:** not reported **Handling of missing data:** not reported
Participants	**Country:** US **Age:** not reported **Gender:** not reported **Inclusion criteria:** 1. diagnosis of POAG, PXG, or PG 2. phakic lens with BCVA 20/30 or worse **Exclusion criteria:** 1. forms of primary or secondary glaucoma not listed above 2. prior glaucoma surgery in the study eye **Diagnoses in participants:** OAG
Interventions	**Intervention 1:** Hydrus Microstent **Intervention 2:** iStent trabecular micro bypass **Length of follow-up:** 2 years
Outcomes	**Primary outcomes:** difference in proportion of participants unmedicated at 12 months following surgery **Secondary outcomes:** mean medication use at 12 and 24 months post procedure **Safety outcomes:** not reported
Starting date	30 December 2013
Contact information	Principal Investigator: Julian Garcia Feijoo, Professor of Medicine, Madrid, Spain
Notes	**Type of study:** awaiting classification, described as "completed" on ClinicalTrials.gov **Funding source:** Ivantis, Inc **Disclosures of interest:** not reported **Publication language:** not reported **Trial registration:** NCT02023242

NCT02024464

Trial name or title	Comparing Hydrus Microstent(TM) to the iStent for lowering IOP in glaucoma patients undergoing cataract surgery
Methods	**Study design:** parallel-group RCT **Unit of randomization:** not reported **Number randomized:** not reported **Unit of analysis:** not reported **Number analyzed:** not reported **Exclusions and losses to follow-up:** not reported **Handling of missing data:** not reported
Participants	**Country:** US **Age:** not reported **Gender:** not reported **Inclusion criteria:** 1. diagnosis of POAG, PXG, or PDG 2. operable age-related cataract with BCVA 20/40 or worse, eligible for phacoemulsification **Exclusion criteria:** 1. forms of primary or secondary glaucoma not listed above 2. prior glaucoma surgery in the study eye **Diagnoses in participants:** POAG, PXG, PDG
Interventions	**Intervention 1:** Hydrus Microstent **Intervention 2:** iStent trabecular micro bypass **Length of follow-up:** 2 years
Outcomes	**Primary outcomes:** IOP at 2 years **Secondary outcomes:** proportion of participants requiring supplemental medication and loss of BCVA at 2 years **Safety outcomes:** not reported
Starting date	31 December 2013
Contact information	Principal Investigator: Iqbal K Ahmed, MD, Mississauga, ON, Canada
Notes	**Type of study:** awaiting classification, described as "active, not recruiting" on ClinicalTrials.gov **Funding source:** Ivantis, Inc **Disclosures of interest:** not reported **Publication language:** not reported **Trial registration:** NCT02024464

NCT02327312

Trial name or title	Multicenter investigation of trabecular micro-bypass stents vs. laser trabeculoplasty
Methods	**Study design:** parallel-group RCT **Unit of randomization:** not reported **Number randomized:** not reported **Unit of analysis:** not reported **Number analyzed:** not reported **Exclusions and losses to follow-up:** not reported **Handling of missing data:** not reported
Participants	**Country:** US **Age:** not reported **Gender:** not reported **Inclusion criteria:** 1. OAG **Exclusion criteria:** 1. active corneal inflammation or edema 2. choroidal detachment, effusion, choroiditis **Diagnoses in participants:** POAG
Interventions	**Intervention 1:** 2 trabecular meshwork micro-bypass stents into the study eye **Intervention 2:** laser trabeculoplasty **Length of follow-up:** 2 years
Outcomes	**Primary outcomes:** IOP reduction up to 2 years **Secondary outcomes:** % IOP reduction up to 2 years **Safety outcomes:** not reported
Starting date	30 December 2014
Contact information	Jeff Wells jwells@glaukos.com
Notes	**Type of study:** awaiting classification, described as "recruiting" on ClinicalTrials.gov **Funding source:** Glaukos Corporation, Laguna Hills, CA, USA provided funding/support **Disclosures of interest:** not available **Publication language:** not available **Trial registration:** NCT02327312

NCT03106181

Trial name or title	A comparison of cataract surgery alone and cataract surgery with iStent
Methods	**Study design:** parallel-group RCT **Unit of randomization:** unclear **Number randomized:** not reported **Unit of analysis:** not reported **Number analyzed:** not reported **Exclusions and losses to follow-up:** not reported **Handling of missing data:** not reported
Participants	**Country:** Australia **Age:** not reported **Gender:** not reported **Inclusion criteria:** 1. age > 18 years 2. diagnosis of mild-to-moderate OAG 3. presence of cataract requiring surgery 4. good understanding of both verbal and written English 5. able to provide informed consent **Exclusion criteria:** 1. recent intraocular surgery within last 3 months 2. other ocular pathology affecting visionInability to complete the elements of the study, e.g. coma, hemodynamic instability, ventilator dependence, that could be of concern in the investigator's judgment 3. non-elective hospitalization within the past 60 days that could be of concern in the investigator's judgment 4. medical illness that in the judgment of the investigator would jeopardize the safe completion of the study. Examples include cancer, chronic inflammatory disease, chronic liver insufficiency, epilepsy, thrombocytosis **Diagnoses in participants:** OAG
Interventions	**Intervention 1:** iStent inject **Intervention 2:** phacoemulsification **Length of follow-up:** 2 years
Outcomes	**Primary outcomes:** IOP reduction up to 2 years **Secondary outcomes:** number of glaucoma medications; participant treatment satisfaction up to 2 years **Safety outcomes:** not reported
Starting date	10 April 2017
Contact information	Jennifer C Fan Gaskin, FRANZCO

NCT03106181 *(Continued)*

	drjfan@gmail.com
Notes	**Type of study:** awaiting classification, described as "recruiting" on ClinicalTrials.gov **Funding source:** Glaukos Corporation, Laguna Hills, CA, USA provided funding/support **Disclosures of interest:** not reported **Publication language:** not reported **Trial registration:** NCT03106181

UMIN000027734

Trial name or title	A randomized study of efficacy of trabecular micro bypass stent with cataract surgery for open angle glaucoma
Methods	**Study design:** parallel-group RCT **Unit of randomization:** not reported **Number randomized:** not reported **Unit of analysis:** not reported **Number analyzed:** not reported **Exclusions and losses to follow-up:** not reported **Handling of missing data:** not reported
Participants	**Country:** Japan **Age:** not reported **Gender:** not reported **Inclusion criteria:** not reported **Exclusion criteria:** not reported **Diagnoses in participants:** OAG
Interventions	**Intervention 1:** iStent during cataract surgeries **Intervention 2:** no iStent during cataract surgeries **Length of follow-up:** 1 year
Outcomes	**Primary outcomes:** IOP post cataract operation at 1, 2, 3, 6, and 12 months **Secondary outcomes:** not reported **Safety outcomes:** not reported
Starting date	12 June 2017
Contact information	Yoshiaki Kiuchi Ykiuchi@hiroshma-u.ac.jp

UMIN000027734 *(Continued)*

Notes	**Type of study:** awaiting classification **Funding source:** Glaukos Corporation, Laguna Hills, CA, USA provided funding/support **Disclosures of interest:** not reported **Publication language:** not reported **Trial registration:** UMIN000027734

AC-IOL: anterior chamber intraocular lens; ALT: alanine aminotransferase; BCVA: best-corrected visual acuity; IOP: intraocular pressure; OAG: open-angle glaucoma; OHT: ocular hypertension; PC-IOL: posterior chamber intraocular lens; PDG: pigmentary dispersion glaucoma; PEXG: pseudoexfoliative glaucoma; PG: pigmentary glaucoma; POAG: primary open-angle glaucoma; RCT: randomized controlled trial; SD: standard deviation; SLT: selective laser trabeculoplasty.

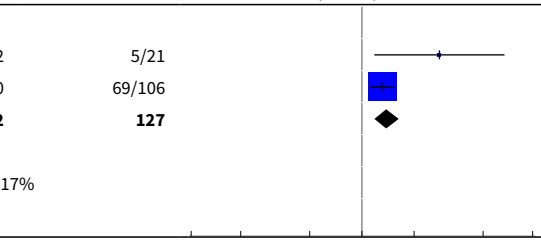
DATA AND ANALYSES

Comparison 1. iStent in combination with phacoemulsification versus phacoemulsification alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Proportion of participants who were drop-free	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 At 6 to ≤ 18 months	2	239	Risk Ratio (M-H, Fixed, 95% CI)	1.38 [1.18, 1.63]
2 Mean change in number of intraocular pressure (IOP)-lowering drops taken per day from baseline	3		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 At ≤ 6 months	1	33	Mean Difference (IV, Fixed, 95% CI)	-0.4 [-0.82, 0.02]
2.2 At 6 to ≤ 18 months	3	315	Mean Difference (IV, Fixed, 95% CI)	-0.42 [-0.60, -0.23]
3 Mean change in IOP	3		Mean Difference (IV, Random, 95% CI)	Totals not selected
3.1 At ≤ 6 months	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
3.2 At 6 to ≤ 18 months (unmedicated IOP)	3		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]

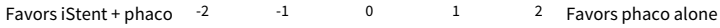
Analysis 1.1. Comparison 1 iStent in combination with phacoemulsification versus phacoemulsification alone, Outcome 1 Proportion of participants who were drop-free.

Study or subgroup	iStent + phaco n/N	Phaco alone n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 At 6 to ≤ 18 months					
Fea 2010	8/12	5/21		5.15%	2.8[1.18,6.64]
Samuelson 2011	85/100	69/106		94.85%	1.31[1.11,1.54]
Subtotal (95% CI)	**112**	**127**		**100%**	**1.38[1.18,1.63]**
Total events: 93 (iStent + phaco), 74 (Phaco alone)					
Heterogeneity: Tau^2=0; Chi^2=3.05, df=1(P=0.08); I^2=67.17%					
Test for overall effect: Z=3.92(P<0.0001)					



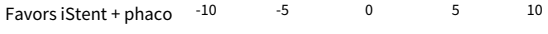
Analysis 1.2. Comparison 1 iStent in combination with phacoemulsification versus phacoemulsification alone, Outcome 2 Mean change in number of intraocular pressure (IOP)-lowering drops taken per day from baseline.

Study or subgroup	iStent + phaco N	iStent + phaco Mean(SD)	Phaco alone N	Phaco alone Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.2.1 At ≤ 6 months							
Fernandez-Barrientos 2010	17	0.1 (0.5)	16	0.5 (0.7)		100%	-0.4[-0.82,0.02]
Subtotal ***	**17**		**16**			**100%**	**-0.4[-0.82,0.02]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.88(P=0.06)							
1.2.2 At 6 to ≤ 18 months							
Fernandez-Barrientos 2010	17	0 (0)	16	0.7 (1)			Not estimable
Samuelson 2011	117	-1.4 (0.8)	123	-1 (0.8)		83.6%	-0.4[-0.6,-0.2]
NCT00721968	25	0.4 (0.8)	17	0.9 (0.7)		16.4%	-0.5[-0.96,-0.04]
Subtotal ***	**159**		**156**			**100%**	**-0.42[-0.6,-0.23]**
Heterogeneity: Tau^2=0; Chi^2=0.15, df=1(P=0.7); I^2=0%							
Test for overall effect: Z=4.41(P<0.0001)							



Analysis 1.3. Comparison 1 iStent in combination with phacoemulsification versus phacoemulsification alone, Outcome 3 Mean change in IOP.

Study or subgroup	iStent + phaco N	iStent + phaco Mean(SD)	Phaco alone N	Phaco alone Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
1.3.1 At ≤ 6 months						
Fernandez-Barrientos 2010	17	-9.3 (4.1)	16	-4.3 (3.1)		-5[-7.47,-2.53]
1.3.2 At 6 to ≤ 18 months (unmedicated IOP)						
Fea 2010	12	-3.2 (3)	21	-1.6 (3.2)		-1.6[-3.78,0.58]
Fernandez-Barrientos 2010	17	-6.6 (3)	16	-3.9 (2.7)		-2.7[-4.65,-0.75]
Samuelson 2011	106	-8.4 (3.6)	112	-8.5 (4.3)		0.1[-0.95,1.15]

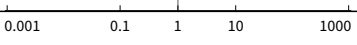


Comparison 2. iStent (or iStent inject) versus medical therapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Proportion of participants who were drop-free	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 At 6 to ≤18 months	2	286	Risk Ratio (M-H, Random, 95% CI)	125.43 [17.80, 883.89]
1.2 At 18 to ≤ 36 months	1	101	Risk Ratio (M-H, Random, 95% CI)	84.65 [5.36, 1336.23]
2 Mean change in intraocular pressure	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1 At ≤ 6 months	1	184	Mean Difference (IV, Random, 95% CI)	0.10 [-0.72, 0.92]
2.2 At 6 to ≤ 18 months	1	184	Mean Difference (IV, Random, 95% CI)	-0.60 [-1.28, 0.08]

Analysis 2.1. Comparison 2 iStent (or iStent inject) versus medical therapy, Outcome 1 Proportion of participants who were drop-free.

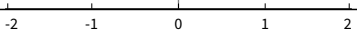
Study or subgroup	Two iStents n/N	Medical therapy n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.1.1 At 6 to ≤18 months					
Fea 2014	90/94	0/91		49.88%	175.28[11.04,2782.31]
Vold 2016	51/54	0/47		50.12%	89.89[5.7,1417.7]
Subtotal (95% CI)	**148**	**138**		**100%**	**125.43[17.8,883.89]**
Total events: 141 (Two iStents), 0 (Medical therapy)					
Heterogeneity: Tau^2=0; Chi^2=0.11, df=1(P=0.73); I^2=0%					
Test for overall effect: Z=4.85(P<0.0001)					
2.1.2 At 18 to ≤ 36 months					
Vold 2016	48/54	0/47		100%	84.65[5.36,1336.23]
Subtotal (95% CI)	**54**	**47**		**100%**	**84.65[5.36,1336.23]**
Total events: 48 (Two iStents), 0 (Medical therapy)					
Heterogeneity: Not applicable					
Test for overall effect: Z=3.15(P=0)					



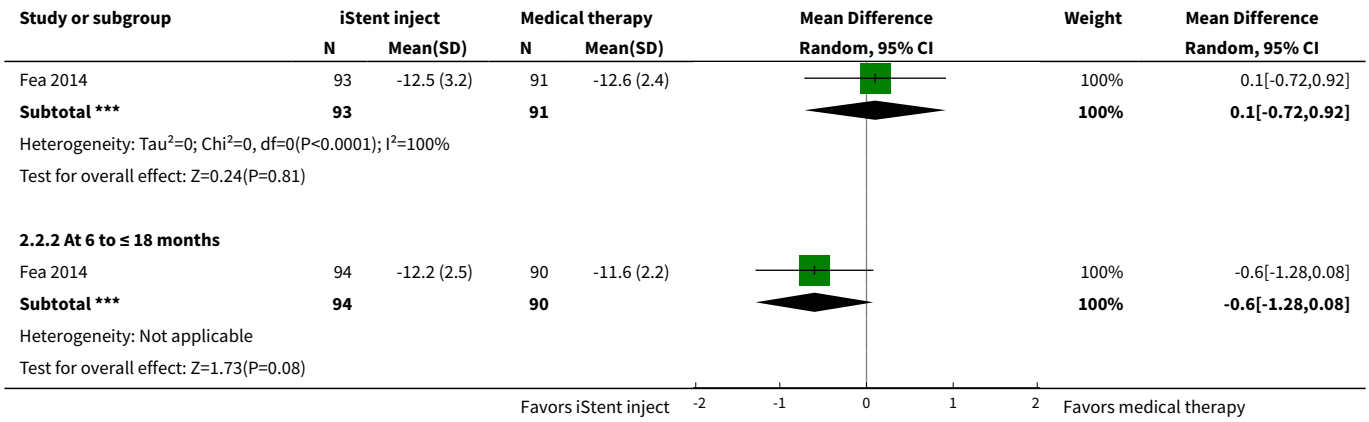
Favors medical therapy — Favors two iStents

Analysis 2.2. Comparison 2 iStent (or iStent inject) versus medical therapy, Outcome 2 Mean change in intraocular pressure.

Study or subgroup	iStent inject N	iStent inject Mean(SD)	Medical therapy N	Medical therapy Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
2.2.1 At ≤ 6 months							



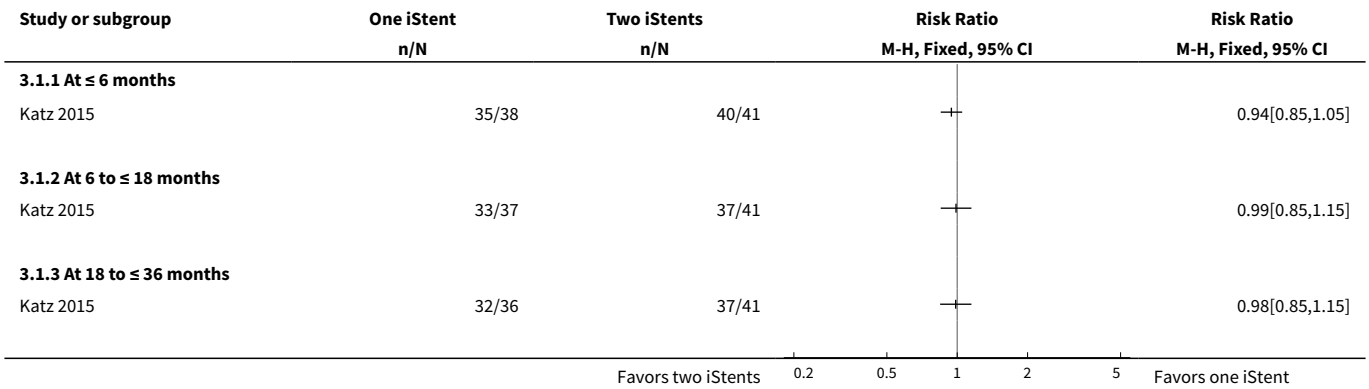
Favors iStent inject — Favors medical therapy

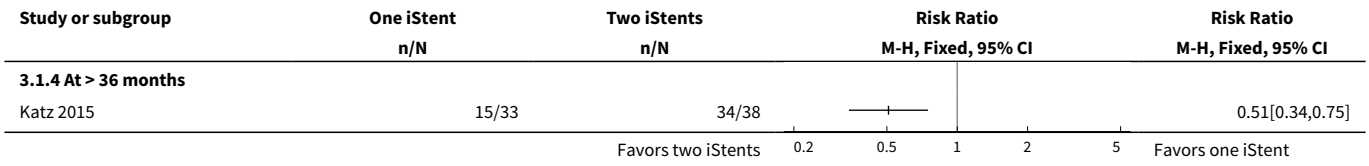


Comparison 3. One iStent versus two iStents

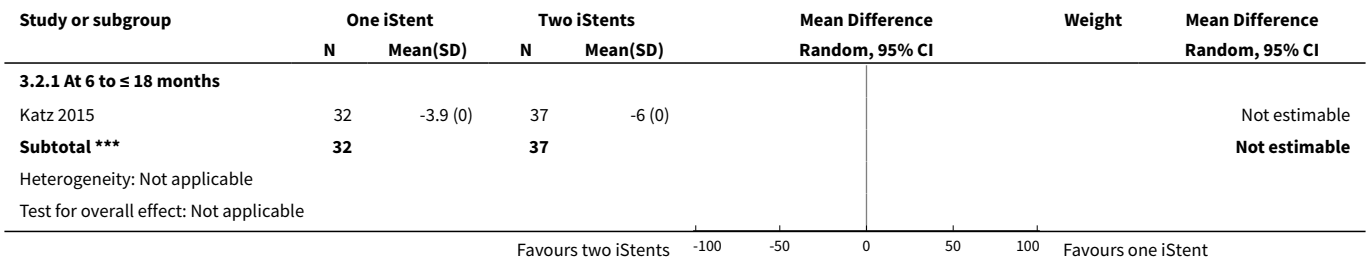
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Proportion of participants who were drop-free	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 At ≤ 6 months	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 At 6 to ≤ 18 months	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 At 18 to ≤ 36 months	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.4 At > 36 months	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Mean change in intraoperative pressure	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1 At 6 to ≤ 18 months	1	69	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 3.1. Comparison 3 One iStent versus two iStents, Outcome 1 Proportion of participants who were drop-free.





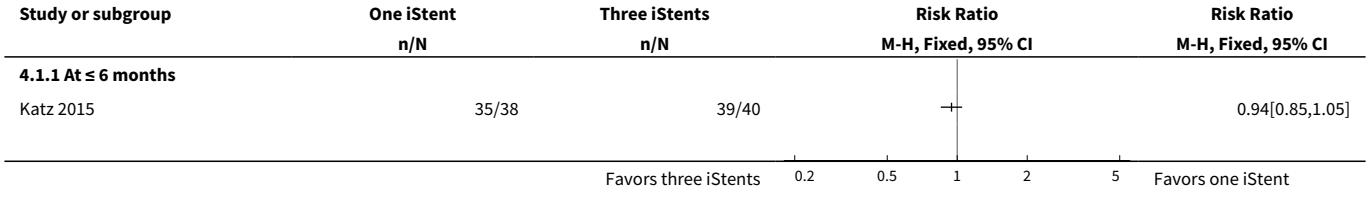
Analysis 3.2. Comparison 3 One iStent versus two iStents, Outcome 2 Mean change in intraoperative pressure.



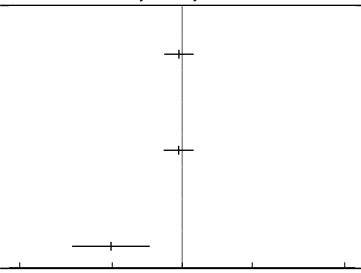
Comparison 4. One iStent versus three iStents

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Proportion of participants who were drop-free	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 At ≤ 6 months	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 At 6 to ≤ 18 months	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 At 18 to ≤ 36 months	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.4 At > 36 months	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Mean change in intraocular pressure	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1 At 6 to ≤ 18 months	1	67	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 4.1. Comparison 4 One iStent versus three iStents, Outcome 1 Proportion of participants who were drop-free.

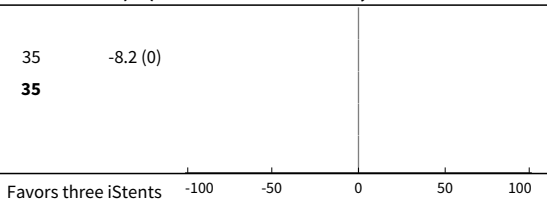


Study or subgroup	One iStent n/N	Three iStents n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
4.1.2 At 6 to ≤ 18 months				
Katz 2015	33/37	35/38		0.97[0.84,1.12]
4.1.3 At 18 to ≤ 36 months				
Katz 2015	32/36	35/38		0.97[0.83,1.12]
4.1.4 At > 36 months				
Katz 2015	15/33	35/38		0.49[0.34,0.73]



Analysis 4.2. Comparison 4 One iStent versus three iStents, Outcome 2 Mean change in intraocular pressure.

Study or subgroup	One iStent N	One iStent Mean(SD)	Three iStents N	Three iStents Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
4.2.1 At 6 to ≤ 18 months							
Katz 2015	32	-3.9 (0)	35	-8.2 (0)			Not estimable
Subtotal ***	**32**		**35**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							



ADDITIONAL TABLES

Table 1. Eligibility criteria of included studies

Study	Diagnosis	Intraocular pressure	Number of glaucoma medication currently taking	Visual acuity (Snellen; BCVA)	Prior incisional glaucoma surgery	Prior laser surgery	Washout period
Comparison 1: iStent in combination with phacoemulsification vs phacoemulsification alone							
Fea 2010	OAG in need of cataract surgery	> 18 mmHg (medicated)	≥ 1	20/80 or worse	Excluded	NR	NR
Fernandez-Barrientos 2010	OHT or OAG in need of cataract surgery	> 17 mmHg and < 31 mmHg (medicated); > 21 mmHg and < 36 mmHg (unmedicated)	≤ 2	20/40 or worse	Excluded	Excluded	Yes
NCT00721968	OAG in need of cataract surgery	NR	NR	NR	NR	NR	NR
Samuelson 2011	OAG, PEXG, or PG, in need of cataract surgery	≤ 24 mmHg (medicated); ≥ 22 mmHg and ≤ 36 mmHg (unmedicated)	≥ 1 and ≤ 3	20/40 or worse	Excluded (except for iridectomy)	Excluded	Yes
Comparison 2: iStent or iStent inject vs medical therapy							
Fea 2014	OAG, PEXG, or PG	≥ 22 mmHg and < 38 mmHg (unmedicated)	1	20/200 or better	Excluded	Included[a]	Yes
Vold 2016	OHT, OAG, or PEXG	≥ 21 mmHg and ≤ 40 mmHg (unmedicated)	0	NR	Excluded	Excluded	NA
Additional comparison: 1 iStent vs 2 iStents vs 3 iStents							
Katz 2015	OAG, PEXG, or PG; and phakic	≥ 18 mmHg and ≤ 30 mmHg (medicated); > 22 mmHg and < 38 mmHg (unmedicated)	2	20/200 or better	Excluded	Included[a]	Yes

[a]As long as the procedure was not performed within 30 days prior to screening.
BCVA: best-corrected visual acuity; OAG: open-angle glaucoma; OHT: ocular hypertension; PEXG: pseudoexfoliative glaucoma; PG: pigmentary glaucoma; NA: not available; NR: not reported.

Table 2. Postoperative complications reported by included studies

Comparison 1: iStent in combination with phacoemulsification vs phacoemulsification alone		
Fea 2010	—	—
Adverse events	"No postoperative stent-related adverse events were observed in these eyes [N = 24] through 48 months. IOP was well controlled in both groups throughout the entire follow-up period; no secondary surgical intervention was required to control IOP."	
Fernandez-Barrientos 2010	2 iStents in combination with phacoemulsification at 1 year	Phacoemulsification alone at 1 year
Stent malposition	Authors noted that "six of the 34 (18%) implanted stents appeared to be malpositioned"	NA
Need for selective trabeculoplasty	0	1/16
NCT00721968	iStent in combination with phacoemulsification at 1 year	Phacoemulsification alone at 1 year
Posterior capsule opacification	4/27	1/17
IOP increase ≥ 10 mmHg vs baseline IOP at any visit	3/27	9/17
Conjunctivitis	3/27	2/17
Corneal abrasion	2/27	1/17
Iritis	2/27	0
Punctate corneal staining	1/27	1/17
Superficial punctate keratitis	1/27	1/17
Blurry vision	1/27	1/17
BCVA loss ≥ 1 line after 3 months postoperative	0	2/17
Eye pain	0	2/17
Retinal detachment	0	1/17
Samuelson 2011	iStent in combination with phacoemulsification at 2 years	Phacoemulsification alone at 2 years
Anticipated early postoperative event (as defined by investigators)	20/116	22/117
Posterior capsule opacification	7/116	12/117

Table 2. Postoperative complications reported by included studies *(Continued)*

Elevated IOP	5/116	8/117
Stent obstruction	5/116	NA
Blurry vision or visual disturbance	4/116	8/117
Stent malposition	3/116	NA
Iritis	1/116	6/117
Conjunctival irritation due to hypotensive medication	1/116	3/117
Disk hemorrhage	1/116	3/117
Comparison 2: iStent (or iStent inject) vs medical therapy		
Fea 2014	iStent inject at 1 year (94 eyes of 94 participants)	Medical therapy at 1 year (98 eyes of 98 participants)
IOP decompensation	1/94	0
Soreness/discomfort	1/94	0
Eye burning	0	1/98
Medical allergy	0	1/98
Secondary glaucoma surgery	1/94	NA
Vold 2016	"Safety was favorable in both groups [Two iStents, N = 54; Medical therapy, N = 47; at 36 months). Two complications were reported during stent insertion in the surgery group, both of which were attributed to subject movement during surgery: one of these subjects had hyphema which resolved by day 1 and one subject had a small iridodialysis which resulted in no postoperative ocular sequelae...In the remaining non-operated subjects, three-year BCVA was 20/40 or better in 6 eyes (2 in stent group and 4 in med group), 20/100 in 1 eye (stent group), and 20/200 in 6 eyes (3 per group). No other post-treatment adverse events were reported in either group."	
Additional comparison: 1 iStent vs 2 iStents vs 3 iStents		
Katz 2015	"No complications occurred intraoperatively or perioperatively, including no hypotony, choroidal effusion, hyphema, nor iridodialysis [One iStent, N=38; two iStents, N= 41; three iStents, N=40]. During 42 months of postoperative follow-up, no device-related or sight-threatening adverse events occurred; furthermore, no eyes required additional glaucoma surgery. In this cohort of almost entirely phakic subjects (117 of 119) with mean baseline age between 62 and 69 years, the most common (and expected) adverse event over 3.5 years of follow-up was progression of preexisting cataract. By Month 42 postoperatively, a total of eight one-stent eyes, five two-stent eyes, and seven three-stent eyes had BCVA loss 1 line due to cataract progression. Of these cases, five one-stent eyes, two two-stent eyes, and three three-stent eyes underwent cataract surgery by Month 42, and their IOP and medication data thereafter were excluded from efficacy analyses; two additional eyes (three-stent group) had cataract surgery shortly after the Month 42 visit."	

BCVA: best-corrected visual acuity; IOP: intraocular pressure; N: number; NA: not available.

Table 3. Summary of financial support of included studies

Study	Pharmaceutical industry involvement	Other financial support
Comparison 1: iStent in combination with phacoemulsification vs phacoemulsification alone		
Fea 2010	Glaukos Corporation provided funding/support (including study devices)	Ricerca Finalizaata della Regione Pimonte 2007
Fernandez-Barrientos 2010	Glaukos Corporation provided funding/support	—
NCT00721968	Glaukos Corporation provided funding/support	—
Samuelson 2011	Glaukos Corporation provided funding/support (Investigators were consultants to Glaukos for the conduct of this study)	—
Comparison 2: iStents vs medical therapy		
Fea 2014	Glaukos Corporation provided funding/support (including study devices, editorial assistance, payment of article processing charges, financial support, and non-study financial support)	—
Vold 2016	Glaukos Corporation provided funding/support (including non-financial, financial, and non-study financial support to some/all authors)	—
Additional comparison: iStent vs 2 iStents vs 3 iStents		
Katz 2015	Glaukos Corporation provided funding/support (including study devices and non-financial, financial, and non-study financial support to some/all authors)	—

APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor: [Glaucoma, Open-Angle] explode all trees
#2 MeSH descriptor: [Intraocular Pressure] explode all trees
#3 MeSH descriptor: [Ocular Hypertension] explode all trees
#4 OAG or POAG or IOP or OHT
#5 simple near/3 glaucoma*
#6 open near/2 angle near/2 glaucoma*
#7 chronic near/2 glaucoma*
#8 secondary near/2 glaucoma*
#9 low near/2 tension near/2 glaucoma*
#10 low near/2 pressure near/2 glaucoma*
#11 normal near/2 tension near/2 glaucoma*
#12 normal near/2 pressure near/2 glaucoma*
#13 pigment near/2 glaucoma*
#14MeSH descriptor: [Exfoliation Syndrome] this term only
#15 exfoliat* near/2 syndrome*

#16 exfoliat* near/2 glaucoma*
#17 pseudoexfoliat* near/2 syndrome*
#18 pseudoexfoliat* near/2 glaucoma*
#19 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18
#20 MeSH descriptor: [Stents] explode all trees
#21 iStent
#22 #20 or #21
#23 #19 and #22

Appendix 2. MEDLINE Ovid search strategy

1. randomized controlled trial.pt.
2. (randomized or randomised).ab,ti.
3. placebo.ab,ti.
4. dt.fs.
5. randomly.ab,ti.
6. trial.ab,ti.
7. groups.ab,ti.
8. or/1-7
9. exp animals/
10. exp humans/
11. 9 not (9 and 10)
12. 8 not 11
13. exp glaucoma open angle/
14. exp intraocular pressure/
15. ocular hypertension/
16. (OAG or POAG or IOP or OHT).tw.
17. (simple$ adj3 glaucoma$).tw.
18. (open adj2 angle adj2 glaucoma$).tw.
19. (primary adj2 glaucoma$).tw.
20. (chronic adj2 glaucoma$).tw.
21. (secondary adj2 glaucoma$).tw.
22. (low adj2 tension adj2 glaucoma$).tw.
23. (low adj2 pressure adj2 glaucoma$).tw.
24. (normal adj2 tension adj2 glaucoma$).tw.
25. (normal adj2 pressure adj2 glaucoma$).tw.
26. (pigment$ adj2 glaucoma$).tw.
27. exfoliation syndrome/
28. (exfoliat$ adj2 syndrome$).tw.
29. (exfoliat$ adj2 glaucoma$).tw.
30. (pseudoexfoliat$ adj2 syndrome$).tw.
31. (pseudoexfoliat$ adj2 glaucoma$).tw.
32. or/13-31
33. exp Stents/
34. istent.tw.
35. 33 or 34
36. 32 and 35
37. 12 and 36

The search filter for trials at the beginning of the MEDLINE strategy is from the published paper by Glanville 2006.

Appendix 3. Embase Ovid search strategy

1. exp randomized controlled trial/
2. exp randomizations/
3. exp double blind procedure/
4. exp single blind procedure/
5. random$.tw.
6. or/1-5
7. (animal or animal experiment).sh.
8. human.sh.
9. 7 and 8
10. 7 not 9

11. 6 not 10
12. exp clinical trial/
13. (clin$ adj3 trial$).tw.
14. ((singl$ or doubl$ or trebl$ or tripl$) adj3 (blind$ or mask$)).tw.
15. exp placebo/
16. placebo$.tw.
17. random$.tw.
18. exp experimental design/
19. exp crossover procedure/
20. exp control group/
21. exp latin square design/
22. or/12-21
23. 22 not 10
24. 23 not 11
25. exp comparative study/
26. exp evaluation/
27. exp prospective study/
28. (control$ or prospectiv$ or volunteer$).tw.
29. or/25-28
30. 29 not 10
31. 30 not (11 or 23)
32. 11 or 24 or 31
33. open angle glaucoma/
34. intraocular pressure/
35. intraocular hypertension/
36. (OAG or POAG or IOP or OHT).tw.
37. (open adj2 angle adj2 glaucoma$).tw.
38. (primary adj2 glaucoma$).tw.
39. (chronic adj2 glaucoma$).tw.
40. (secondary adj2 glaucoma$).tw.
41. (low adj2 tension adj2 glaucoma$).tw.
42. (low adj2 pressure adj2 glaucoma$).tw.
43. (normal adj2 tension adj2 glaucoma$).tw.
44. (normal adj2 pressure adj2 glaucoma$).tw.
45. (pigment$ adj2 glaucoma$).tw.
46. exfoliation syndrome/
47. (exfoliat$ adj2 syndrome$).tw.
48. (exfoliat$ adj2 glaucoma$).tw.
49. (pseudoexfoliat$ adj2 syndrome$).tw.
50. (pseudoexfoliat$ adj2 glaucoma$).tw.
51. or/33-50
52. Stent/
53. istent.tw.
54. 52 or 53
55. 51 and 54
56. 32 and 55

Appendix 4. ISRCTN search strategy

iStent

Appendix 5. ClinicalTrials.gov search strategy

iStent

Appendix 6. WHO ICTRP search strategy

iStent

Appendix 7. FDA search strategy

istent AND random OR randomly OR randomised OR randomized

Appendix 8. Data on study characteristics

Mandatory items		Optional items
Methods		
Study design	• **Parallel group RCT***i.e. people randomized to treatment* • **Within-person RCT***i.e. eyes randomized to treatment* • **Cluster RCT***i.e. communities randomized to treatment* • **Cross-over RCT** • Other, specify	Number of study arms Method of randomization Exclusions after randomization Losses to follow-up
Eyes Unit of randomization/unit of analysis	• **One eye included in study**, *specify how eye selected* • **Two eyes included in study, both eyes received same treatment**, *briefly specify how analyzed (best/worst/average/both and adjusted for within person correlation/both and not adjusted for within person correlation) and specify if mixture of one eye and two eyes* • **Two eyes included in study, eyes received different treatments,***specify if correct pair-matched analysis done*	Number randomized/analyzed Method of masking How were missing data handled? *e.g. available case analysis, imputation methods* Reported power calculation (Y/N)*, if yes, sample size and power* Unusual study design/issues
Participants		
Country	—	Setting Ethnic group Method of recruitment Participation rate Equivalence of baseline characteristics (Y/N) Diagnostic criteria
Total number of participants Number (%) of men and women Average age and age range	*This information should be collected for total study population recruited into the study. If these data are reported for the people who were followed up only, please indicate.*	
Inclusion criteria	—	
Exclusion criteria	—	
Interventions		
Intervention (n=) Comparator (n=) ***See MECIR 65 and 70***	• Number of people randomized to this group • Intervention name • Comparator name • Specify whether phacoemulsification, or other intervention, performed at same time as intervention	iStent or iStent inject surgical parameters, *e.g. degrees of meshwork ablated, electrosurgical power* Comparator parameters, *e.g. dosage of drugs*
Outcomes		
Primary and secondary outcomes *as defined in study reports* ***See MECIR R70***	• Proportion of participants who were drop-free at 2 years' follow-up • Mean change in number of IOP-lowering drops taken per day from baseline to 2 years' follow-up	Planned/actual length of follow-up

(Continued)

- Mean change in IOP from baseline to 2 years' follow-up
- Health-related quality of life measures at 2 years' follow-up
- Intraoperative complications

Adverse events reported (Y/N)

Notes		
Date conducted	Specify dates of recruitment of participants mm/yr to mm/yr	Full study name: *(if applicable)*
Sources of funding	—	Date of publication
Declaration of interest ***See MECIR 69***	—	Reported subgroup analyses (Y/N) Were trial investigators contacted?

CONTRIBUTIONS OF AUTHORS

JL, AB, and TL designed and wrote the review.
JL, LW, and TL screened studies for inclusion.
JL and LW extracted data from studies.
JL, AB, LW, and TL drafted the review and will be responsible for updates.

DECLARATIONS OF INTEREST

JL: This Cochrane Review was prepared while Dr. Le was a doctoral candidate at the Johns Hopkins Bloomberg School of Public Health. The opinions expressed in this article are the author's own and do not reflect the view of the National Institutes of Health, the Department of Health and Human Services, or the United States government.
AB: none.
LW: none.
TL: none.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- National Eye Institute (NEI), National Institutes of Health (NIH), USA.

  Cochrane Eyes and Vision US Project (and JL during his time with the Project) is supported by cooperative agreement UG1EY020522, NEI, NIH
- National Institute for Health Research (NIHR), UK.

  * Richard Wormald, Co-ordinating Editor for Cochrane Eyes and Vision (CEV) acknowledges financial support for his CEV research sessions from the Department of Health through the award made by the National Institute for Health Research to Moorfields Eye Hospital NHS Foundation Trust and UCL Institute of Ophthalmology for a Specialist Biomedical Research Centre for Ophthalmology.
  * This review was supported by the National Institute for Health Research, via Cochrane Infrastructure funding to the CEV UK editorial base.

  The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS or the Department of Health.
- National Institute of Aging (NIA), National Institutes of Health (NIH), USA.

  JL is supported by the Epidemiology and Biostatistics of Aging Training Program, Grant Number T32 AG000247 from the NIA, NIH.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The protocol for this review did not specify time windows for the outcomes analyzed. Working with other author teams of the MIGS Consortium, we clarified time windows of interest as short-term (six months or less), medium-term (six to 18 months or less), long-term (greater than 18 months but less than or equal to 36 months), and over 36 months. When conducting meta-analyses, we used fixed-effect models in lieu random-effects models due to small numbers of randomized controlled trials included. Given that the iStent devices were approved in people undergoing cataract surgery (phacoemulsification), we regarded combined phacoemulsification and MIGS procedure versus phacoemulsification alone as a separate comparison instead of a subgroup analysis.

INDEX TERMS

Medical Subject Headings (MeSH)

*Glaucoma Drainage Implants; *Stents; *Trabecular Meshwork; Antihypertensive Agents [administration & dosage]; Combined Modality Therapy [methods]; Glaucoma, Open-Angle [*surgery]; Ocular Hypertension [therapy]; Ophthalmic Solutions [administration & dosage]; Phacoemulsification; Randomized Controlled Trials as Topic

MeSH check words

Aged; Aged, 80 and over; Female; Humans; Male; Middle Aged